A Review of Volume, Costs, Patient-Visits and Impacts

The Case of INR-testing in Norway 2009-2011

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Summary

Objective

Estimate societal costs relating to INR-testing for the year 2009 in Norway and the numbers of INR tests performed by GPs and private specialists during the periods of 2009, 2010 and 2011. I also aim to calculate the number of INR-test-related GPs/ private specialist visit-reductions due to the introduction of the new oral anticoagulants (NOACs) for Norwegian patients for the same period. I will further examine if such reduced visits for atrial fibrillation patients have any impact on the cost- effectiveness of NOACs compared to Warfarin by evaluating their incremental net health benefit.

Finally, I will calculate the 2013 total usage- costs for Dabigatran, Apixaban and Rivaroxaban, compared to using Warfarin.

Background

Venous Thromboembolism (VT) represents the third most common cardiovascular disease after myocardial infarction and stroke. Incidence rate of a first VT is estimated at 1-2 events per1000 person-years. Warfarin therapy is standard but hazardous and requires continuous INR monitoring. Replacement NOACs do not need any INR monitoring but they are considerably costly. Studies evaluating cost- effectiveness of NOACs compared to warfarin, with respect to numbers of such reduced visits for INR- patients are uncertain and limited.

Methods and Data

Quantitative Survey-based study in 2010 targeted at different Norwegian hospitals within the South East Regional Health Enterprise (SØ-HF), literature and internet search using different relevant databases. INR-test raw data for 2009-2011 was obtained from the Norwegian Health Economics Administration (HELFO/ Helseøkonomiforvaltningen). New oral anticoagulants (NOAC) data for the period 2009-2013 was obtained from the Norwegian Prescription Database (NorPD/Reseptregisteret).

Linear regression was used to estimate the trend of oral anticoagulants prior to the introduction of NOACs

Results

Estimated societal costs relating to INR testing in 2009 were about 700 million NOK. There is an actual increase (about 12%) in the numbers of performed INR tests by GPs and private specialists between the years 2009-2011. Estimated future reduction in costs related to INR-tests were found to be 66-86 million NOK, which are only half of such costs presented in the HTA-2013 report. In 2013 about 255 million NOK was used on NOACs and 79 million NOK

on Warfarin. Reductions in the number of GPs visits for INR –patients have insignificant impact on the cost effectiveness of NOACs compared to warfarin.

Interpretation

Reductions in the numbers of INR-tests/ GP visits presented in the HTA 2013 report for patients with atrial fibrillation were unrealistically high, which means that at the introduction of NOACs, the Norwegian Health Ministry should have allocated about 100 million NKR extra in its budget, to compensate for overestimated savings associated with reduced doctor-visits'costs when approving the use of NOACs in Norway. For atrial fibrillation patients, the incremental net health benefits associated with reductions in the number of GPs/ private specialists visits due to using NOACs in their treatment is far too small, and has no apparent effect on the cost effectiveness of NOACs compared to Warfarin.

1.1 Acronyms

AF	Atrial Fibrillation indicating abnormal heart rhythm
CHA2DS2-VASc Risk score.	Different risk factors indicate increased risk of stroke among patients with atrial fibrillation. Total score ranges from 0 to 9, with the following scoring per risk factor: Congestive heart failure = 1, Hypertension = 1, Age>75 = 2, Prior Stroke/TIA/thromboembolism = 2, Vascular disease = 1, Age65-74 = 1, Diabetes mellitus = 1, **Sex (female) =1.**
DVT	Deep Vein Thrombosis
HELFO	The Norwegian Health Economics Administration. It is a sub-ordinate institution directly linked to the Norwegian Directorate of Health. HELFO is responsible for direct payments to different health service providers,and for some reimbursement for certain medicines
HTA	Health technology assessment. Multi-disciplinary containing a systematic review of the technology and an economic Evaluation. Implications for economic and policy settings and overall organizational consequences
INHB	Incremental net health benefit. Difference in NHB between two interventions
INR	International Normalized Ratio indicating levels of agglutination of blood. Ideally between 2.0-3.0. Slight variations according to health state context of the patient

NHB	NHB Net Health Benefit. In a decision-making process, a positive NHB suggests that the intervention represents good value for money
NOACs	New Oral Anticoagulants. In this study, only Apixaban, Rivaroxaban and Dabigatran are included.
NoMA	The Norwegian Medicines Agency, Approves the use of new drugs and their reimbursement costs
PE	Pulmonary Embolism
QALY	Quality-adjusted life-year. A measure of health outcomes combining quantity and quality of life by assigning to each year of life a weight from 1 (perfect health) to 0 (state judged equivalent to death) dependent on the individual's health related quality of life during that year
TP	Thrombosis Prophylaxis
VTE	Venous Thromboembolism

Preface

I would like to extend my deepest thanks and gratitude to my supervisor Professor Ivar Sønbø Kristiansen for his professional supervision and personal involvement in this research project. Ivar has been instrumental in guiding my research interests to venous thromboembolic diseases, their prevalence, therapies and costs. His lectures and discussion sessions were an eye-opener for me to the value of this research-domain as a whole, and to the wide spectrum available when choosing different research designs and methods. Ivar's personal touch always added to the quality of my reports, and his friendly smile, always welcoming through his wide-open office door, irrespective of an always full and busy schedule. Takk Ivar.

My special thanks to my co-supervisor Associate Professor Torbjørn Wisløff for his tremendous help, at short notice during the critical phase of this study. Our discussions helped me to make sense of the raw-data at hand and of its potential when performing data analysis. Your help Torbjørn was invaluable. Thanks again.

My special thanks to everyone at the Department of Health Economics, Policy, and Management for supplying both material infrastructure and human resources to facilitate this research project and for including me into your professional network. Sincere thanks to student advisor Birthe Neset for handling the many unforeseeable delays relating to delivery deadlines of this thesis. My great appreciations go to my fellow students at this program. We surely made many beautiful and lasting bonds that hopefully will last with us, always.

Finally, my thanks to my own family for their practical and mental support throughout the whole of this period. My wife Lisbeth, always loving and encouraging, our daughters Amalie and Viktoria and our sons Aleksander and Fredrik for making every day a joyous one and for giving my life a healthy and meaningful perspective. My eternal thanks to my brothers Sami, Samir and Elias, and to my sisters Salwa and Hana for always being there for me, no matter what.

Love you all,

Hani

Contents

1. Aim

The first aim of this study is to estimate the numbers of different International Normalized Ratio (INR) tests performed in Norway, and their societal costs for the year 2009. Based on raw-data for INR testing obtained from the Norwegian Health Economics Administration (HELFO/ Helseøkonomiforvaltningen), which is a sub-ordinate institution directly linked to the Norwegian Directorate of Health. I will also examine any trends present in the numbers of INR tests performed by GPs and private specialists during the periods of 2009, 2010 and 2011.

The second aim of this thesis is to examine whether assumed reductions in the numbers of INR-tests performed per Atrial Fibrillation(AF) patient per year are realistic, as they were presented by the pharmaceutical industry and the Norwegian Knowledge Centre for the Health Services (Kunnskapssenteret) with respect to estimating costs associated with the introduction of different new oral anticoagulants (NOACs) in 2013.

The third aim is to examine if such reduced numbers of visits for AF patients have any impact on the cost- effectiveness of NOACs compared to Warfarin when evaluating their incremental net health benefit (INHB) values.

Key terms: International Normalized Ratio (INR), societal costs, reduced GPs/ private specialist costs, new oral anticoagulants (NOACs), and incremental net health benefit (INHB).

2. Introduction

This thesis is structured as follows:
Firstly, I present overall general view relating to prevalence of cardiovascular disease (CVD), globally, regionally and locally. *Secondly*, I will focus on different forms of thromboembolic diseases, giving a brief description of their main causes, symptoms, tests and some alternative treatments in the form of warfarin and other newer oral thrombin inhibitors (NOACs). *Thirdly*, I will focus on the role of International

Normalized Ratio (INR) monitoring for patients using warfarin based medication and estimate the total number of INR tests performed in different Norwegian hospitals, general practitioners (GPs) and specialists' private on-site laboratories and other commercial laboratories in order to estimate INR societal costs for 2009, in Norway. *Fourthly,* based on INR raw-data obtained from the Norwegian Health Economics Administration (HELFO/ Helseøkonomiforvaltningen) for the years 2009, 2010 and 2011, I will study any trends present in the numbers of INR tests performed by GPs and private specialists for this period. Based on data obtained from the Norwegian Prescription Database (NorPD) Reseptregisteret) for the period 2009-2013. I would then present my "reduced-GPs visits" findings and argue whether the assumed reductions in the numbers of INR-tests performed per Atrial Fibrillation (AF) patient per year are realistic, as they were presented by the pharmaceutical industry and the Norwegian Knowledge Centre for the Health Services (Kunnskapssenteret) with respect to estimating costs associated with the introduction of different new oral anticoagulants (NOACs) in 2013. I will further examine if such reduced numbers of visits for AF patients have any impact on the cost- effectiveness of NOACs compared to Warfarin when evaluating their incremental net health benefit (INHB) values.
I will finally estimate reduced visits-costs for Dabigatran, as an example, at the time Boehringer Ingelheim applied for Pradaxa approval.

The study itself is divided into **3 sections**.

The ***first*** **section** relates to estimating the total number of INR tests performed in Norway and their societal costs for 2009, based on survey data collected during 2010 in collaboration with Professor Ivar Sønbø Kristiansen at the University of Oslo, Department of Health Management and Health Economy (Murad, H & Kristiansen, I. S. 2010).
The ***second section*** relates to identifying the numbers of INR tests performed in 2009, 2010 and 2011 by different GPs and private specialists based on raw data obtained from the Norwegian Health Economics Administration (HELFO/ Helseøkonomiforvaltningen). Based on this I will also examine any patterns/ differences between the numbers of performed INR tests by GPs and private specialists between 2009 and 2011.

The ***third section*** relates to calculating any reductions of INR-tests related number of GPs/ private specialist visits per Atrial Fibrillation (AF) patient per year in 2013, and to estimate use- costs associated with using some of the new oral anticoagulants (NOAC) namely, Dabigatran, Apixaban and Rivaroxaban, compared to using Warfarin in 2013. Based on my calculated numbers of GPs/ private practitioners reduced visits for INR-patients, I will evaluate whether reduced numbers of visits for AF patients have any impact on the cost- effectiveness of NOACs compared to Warfarin when evaluating their incremental net health benefit (INHB) values as they appeared in the Kunnskapssenterets 2013 HTA report. This part of the study is done in collaboration with Torbjørn Wisløff, Associate Professor, and a co-author of the HTA report nr 5-2013.

Data for this part of my study is extracted from the Norwegian Prescription Database (Reseptregisteret).

Embolic disease is a cardiovascular disease in either arteries or veins that disrupts the natural flow of blood within the circulatory system, thus affecting the transport of blood-oxygen to different organs in the body. Both stroke and cardiovascular diseases (CVDs) represent major causes of disability and deaths worldwide (WHO, 2011).
In 2009 about 17 million people died from CVDs, where over 7 million deaths were due to coronary heart disease and about 6.2 million deaths were due to stroke (WHO, 2011). CVDs are expected to remain the leading cause of death (Yach D.et al., 2004)) with a postulated increase reaching an estimated 23.3 million by 2030. Some behavioral risk factors of heart diseases represent about 80% of causes leading to cerebrovascular disease and CVD (WHO, 2011). These include heavy smoking, excessive alcohol drinking, poor diet, high blood pressure and lack of physical activities, amongst others. Some underlying determinants of CVDs relate to genetic disposition, population aging, economic and social changes (Roger et al, 2012). Assuming similar exposures to different risk factors, Men develop CVDs about 10 years earlier than women (Heron, 2008).
In Europe, CVDs cause over 4 million deaths every year (47% of total deaths) and over 1.9 million deaths in the European Union, EU (40% of total deaths), where women represent about 55% and men about 43% of total CVDs deaths (WHO, 2011; Yach et al., 2004).

Overall CVDs are estimated to cost the European Union (EU) economy about €196 billion a year. In the EU, 54% of all costs are related to health care costs, 24% due to productivity losses and 22% due to the informal care of patients with CVD (OECD, 2012).

In Norway, statistics from the National Registry of Cardiovascular Diseases/ Hjerte- og karregisteret- (HKR, 2011) indicate that annually, about 15 000 people suffer from acute myocardial infarction, ca 50% of them under 74 years and about 13 000 suffer from acute stroke, half of them under 76 years old. . In 2012, 5260 people died of ischemic heart disease relating to angina pectoris and myocardial infarctions, whereas 3180 people died as a result of a stroke. 1 out of 4 acute stroke patients had developed stroke earlier (Ellekjær H & Selmer R, 2007). During the first 8 months of 2012, 10 500 people suffered an acute myocardial infarction and about 9000 had an acute stroke as a main diagnosis (HKR, 2012.

Data from the National Health Institute/ FHI shows that between 1970 and 2012, there is a progressive decline in the number of deaths due to both CVD and Stroke, probably due to better early diagnosis and modern therapies (Appendix 1, figures 1, 2, 4). No explicit data was found to reflect actual levels of AT incidences in Norway.

The HUNT study from Nord-Trøndelag (2006-2008) shows that about 55 000 people in Norway live with a stroke today and due to ageing populations, this number is estimated to rise to 110 000 in the year 2030 (Statens helsetilsyn).

In 2012, 4852 people died from ischemic heart disease, representing a 38% reduction in the last 10 years (SSB, 2013).

There are limited studies reflecting total costs associated with CVD prevalence, while social costs associated with stroke, in Norway, are estimated around 7-8 milliard kroner annually (Fjærtoft H & Indredavik B, 2007).

A major risk factor attributed to onsets of stroke and other cardiovascular events is Atrial Fibrillation (AT), which simply means, disturbances to normal heart-rhythms. If untreated, complications associated with AT might lead to disability or fatal stroke. It affects about 1-2% of the Norwegian population and it is estimated that between (70-82 000) patients suffer from AT (Helsedirektoratet Rapport, 04.2010). Standard therapy, so far, has been the use of the oral anticoagulant Warfarin. This is hazardous due to increased risks of bleedings since Warfarin interferes with normal blood

clotting mechanisms and reduces blood coagulation time, which might have severe health consequences. It is therefore necessary to monitor warfarin effect through an International Normalized Ratio test (NR), which measures prothrombin time (PT) as an indicator of blood clotting-process. Normally, INR range is set at (2.0-3.0). INR value of less than 2.0 target range increases the risk of clotting and a range value over 3.0 increases the risk of hemorrhage.

Such INR-test related costs are very high, representing severe burdens on national health budgets. IN 2009, Estimated INR-test costs in Norway were about NOK 70 million, and societal costs associated with INR testing were estimated at about NOK 705 million (Kristiansen I.S, report of 30.07.2010).

New oral anticoagulants (NOACs), including Dabigatran, Rivaroxaban and Apixaban are being increasingly used as replacements to warfarin therapy. These do not require any INR monitoring, however they are more costly to use. Issues relating to their specific efficacy, context of use, and reimbursement costs are widely debated and studied since they also have a huge burden on total health costs and national budgets.

3. Background

Different disorders of the blood vessels supplying blood to the heart, brain, lungs, arms and legs may be caused by atherosclerosis, heredity, hypertension and inflammations , such as rheumatic fever, which is caused by streptococcal bacteria, amongst many other causes, often lead to myocardial infarctions and strokes in affected patients.(Heron, 2012)

Source: http://my.clevelandclinic.org/heart/disorders/vascular/whatis.aspx (18.04.2014)

3.1 Atherosclerosis

Atherosclerosis is a condition caused by deposits of low density lipoproteins (LDP)/ fatty deposits/ plaques in the inner walls of blood vessels resulting in the formation of blockages/ clots in blood supply to either the heart or the brain causing disturbances and restrictions to blood flow. Such progressive thickening of blood vessels' walls may result in different possible disease conditions, including amongst others, deep vein thrombosis (DVT), pulmonary embolism (PE) or systemic embolism (SE) and ischemic stroke (27). There are

different morphologies describing the usual sequence of lesion progression from Type I to type V lesions, depending on the levels of accumulated lipids and calcium (Stray H C, 1989). Symptoms may include chest pain and pressure/angina, sudden numbness in arms or legs, slurred speech, amongst others, which symbolizes transient ischemic attack (TIA) that may develop to a stroke.

Source: http://www.mayoclinic.org/diseases-conditions/arteriosclerosis atherosclerosis/basics/symptoms/con-20026972 (18.04.2014)

The following figures below, figures1-3 show different examples of atherosclerosis:

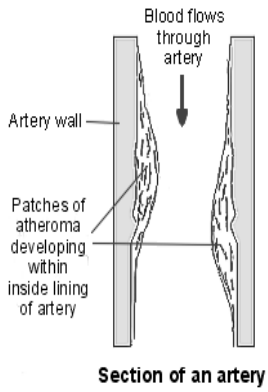


Figure 1. Development of atheroma/ hardening of the arteries which might lead to the formation of blood clot/ thrombosis, that blocks blood flow and might lead to stroke or myocardial infarction.

Source: http://www.patient.co.uk/health/preventing-cardiovascular-diseases (16.04.2014)

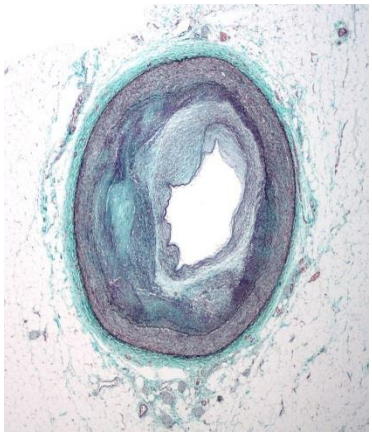


Figure 2. Micrograph of a cardiac artery showing luminal narrowing due to atherosclerosis.

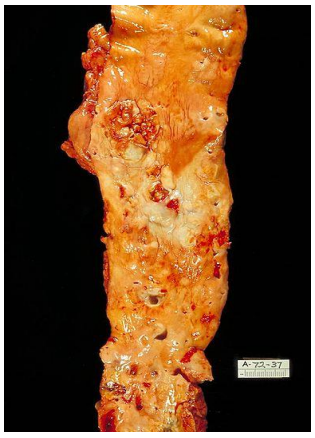


Figure 3. Severe atherosclerosis of the aorta.

Source: http://en.wikipedia.org/wiki/Atherosclerosis (16.04.2014)

Atherosclerosis is usually detected by angiography or ultrasound examination which displays diferent levels of stenosis, as shown in figure 4 below,

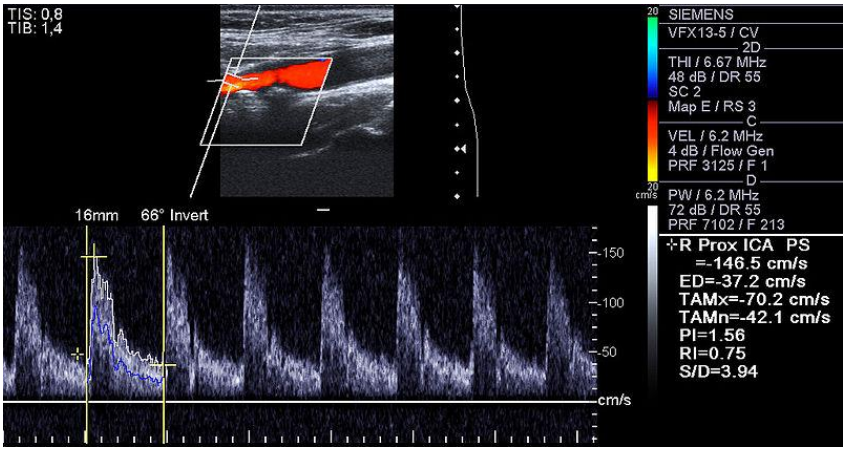


Figure 4. Doppler ultrasound of right internal Carotid artery showing about 70% stenosis due to plaques formation.

Source: http://en.wikipedia.org/wiki/Atherosclerosis (accessed 02.06.2014)

Typical treatment incorporates different forms of medications, including statins and anticoagulants, angioplasty, diet and exercise.

3.2 Major manifestations of Thromboembolic disease

Thromboembolism occurs when a thrombus breaks out from a blood vessel and dislodges in another vessel, for example, the brain, which may result in stroke, or in the lungs, causing pulmonary embolism.

Thromboembolic disease manifests itself in many forms, including Venous Thrombo Embolism (VTE), Non Rheumatic Atrial Fibrillation (AT), Thrombosis Prophylaxis and due to Mechanical Heart Valves.

3.2.1 Venous Thromboembolism

Venous thromboembolism (VTE) is a disease resulting from the formation of a thrombus in a vein. It includes both deep vein thrombosis (DVT) and pulmonary embolism (PE).

3.2.2 Deep Vein Thrombosis (DVT)

DVT is a blood clot in the veins of the lower limbs/ legs and is often associated with pulmonary emboli develops often in the calf veins, leading to "hypoxemia"/ low concentration of Oxygen in the blood, and disturbances of blood flow through the circulatory system. Fibrin attaches to the endothelium of blood vessel causing structural blockages to normal blood flow. Complications can be serious and about 10% lead to pulmonary emboli.

Incidence, about 1: 1000. Therapy is through the use of anticoagulants or surgery)

Source: http://en.wikipedia.org/wiki/Deep_vein_thrombosis (accessed 02.06.2014)

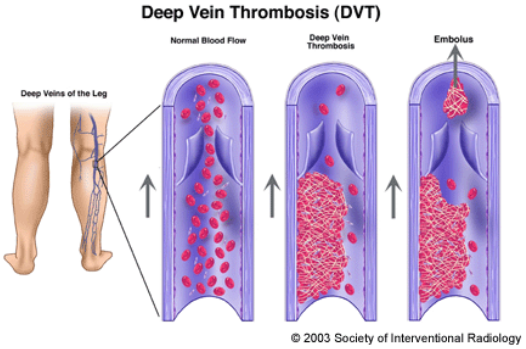


Figure 5. Showing the development of deep vein thrombosis in the leg.

Risk factors include immobility, recent surgery, coagulation abnormalities, obesity, amongst many others.

Source: http://www.sirweb.org/patients/deep-vein-thrombosis/ (accessed 07.06.2014)

3.2.2 Pulmonary Embolism(PE)

This is simply a blood clot in the lungs. "Thrombus formation within the circulatory system that obstructs pulmonary blood flow in the pulmonary artery or any of its branches" as shown in figure 6 below.

http://heartdisease.about.com/od/lesscommonheartproblems/a/Pulmonary-Embolus.htm (accessed 07.06.2014)

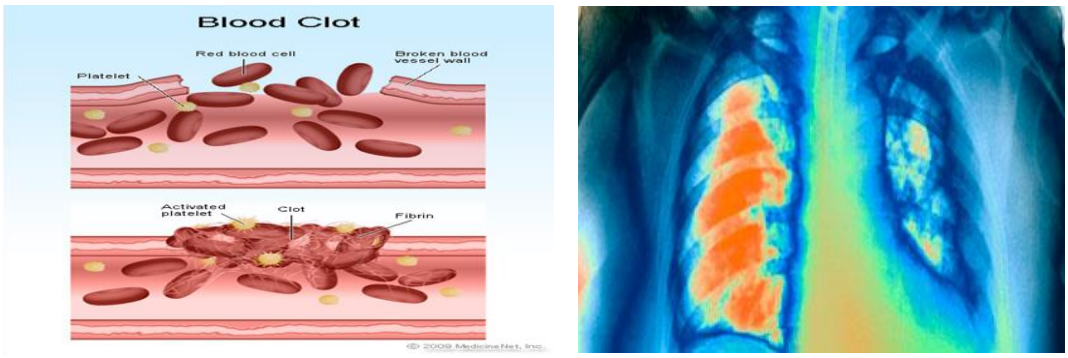


Figure 6. Blood clot formation, and a blocked artery transporting blood to the lungs

Source: http://www.medicinenet.com/pulmonary_embolism/article.htm (accessed 07.06.2014)

: http://www.nhs.uk/conditions/pulmonary-embolism/Pages/Introduction.aspx

It is caused by a blockage to a pulmonary artery either from a clot, or occasionally from air. It is diagnosed by means of clinical examination, arterial blood gas measurements, chest- x ray, ultrasound tests and venography. Main treatment, depending on causes is through thrombolytic therapy using anticoagulants. About 10 % of patients die during the first hours of onset.

Risk factors include hyper coagulation, for example in pregnancy, lack of physical activity deficiency of proteins C, S, and many other causes. Management treatment is through the use of anticoagulants.

Source: http://medical-dictionary.thefreedictionary.com/pulmonary+embolism (accessed 07.06.2014)

3.2.4 Non-Rheumatic Atrial Fibrillation (AF)

Atrial fibrillation (AF) is an irregularity of heart beats due to increased right atrial pressure with a frequency of 350-480 per minute , leading to filtering of the atrio-ventricular node, resulting in irregular QRS complexes at irregular intervals, as shown in *figure 7* below (Camm AJ et al., 2010). This irregularity results in an uneven blood flow and increased risk of blood clot formation. Clots may be carried through the blood flow causing stroke or systemic embolism in different parts of the body.

There are no clear patterns of indications. Some “bouts” of fibrillation may occur at night and after meals or exercise. In the absence of other cardiac disease, it is often termed as “lone

atrial fibrillation". It affects 1-2 % of populations in developed countries, including Norway (Andersen et al., 2010). It is more prevalent in men and prevalence increases in ageing populations, reaching about 10 %. About 65 000 Norwegians are estimated sufferers of AF

(Camm AJ et al., 2010) Different risk factors include diabetes, hypertension, chronic renal and heart diseases, amongst many others. It may be triggered by venous thromboembolism or pulmonary embolism. It increases risks of ischemic stroke, and doubles "all-cause mortality" (Kannel WB & Benjamin EJ, 2008). Different circumstantial evidence and weak associations, there is an understanding of a link between venous thromboembolism and future atrial fibrillation (Kline et al., 2009)

Figure 7. ECG display of Heart beats for normal and atrial fibrillation conditions

Source: http://medxforum.com/vb/showthread.php?803-By-Videos-Atrial-Fibrillation-made-Easy (accessed 07.06.2014)

In addition to ECG, echocardiography, chest x-ray, Holter monitoring, exercise tests, and electrophysiology tests may be used for the diagnosis of AF. It is managed through different pharmacological interventions, including Beta-blockers and Calcium-channel blockers to control heart rate and heart rhythm, medicines to prevent blood clots, including heparin, aspirin, warfarin and new oral anticoagulants, such as dabigatran, rivaroxaban and apixaban. Acute onset of AF is managed through electrical and/ or pharmacological cardioversion using, for example, Amiodarone and class 1c agents, and through surgery. Therapy is often complex depending on the general health condition of patients and contra-indications of other diseases (Nieuwlaat et al., 2005; NICE, 2006).

3.2.5 Thrombosis Prophylaxis

Optimal treatments and methods are uncertain. Warfarin and low molecular weight Heparins are used as prophylactic agents. The National Institute for Health and Clinical Excellence (NICE) sets up different guidelines for reducing risks of VTE. About 30 % of surgical patients develop VTE. Risk of fatal embolism is 1-5%. Compression Stockings are often used. Rivaroxaban is licensed now for use in orthopedic prophylaxis (NICE, 2010). Post operative DVT is often asymptomatic, and Routine use of thromboprophylaxis is recommended in patients over 40 years old. About 3% of orthopedic surgery patients develop DVT . Vascular surgery without prophylaxis gives about 20 % DVT (Hollyoak et al., 2001)

3.3 Warfarin

Warfarin is vitamin K antagonist and it is effective as an oral anticoagulant drug for patients suffering from thrombosis . It blocks the function of vitamin K clotting factors II (Prothrombin), VII(Proaccelerin), IX and X (Stuart-Prower) , thus delaying the production of vitamin K and clotting time. It is a racemic mixture of two active isomers (R and S- isomers), with equal amounts of left- and right-handed enantiomers of a chiral molecule (Karlsson et al., 2007), as shown in figure 8 below. The S- isomer 2-5 times more potent than the R-isomer in producing an anticoagulant response (Hirsh et al., 2003).

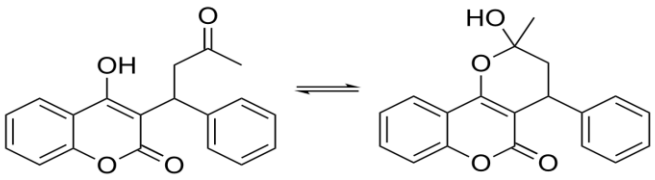


Figure 8. Acyclic (left) and cyclic (right) tautomer forms of warfarin

Source: http://en.wikipedia.org/wiki/Warfarin (accessed 02.05.2015)

Its activity depends on clearance of clotting factors from the blood after administration of the drug and used for preventing thromboembolism through the inhibition of vitamin K epoxide reductase enzyme that recycles oxidized vitamin K to its reduced form after carboxylation activity (Ansell et al., 2008) as shown in figure 9 below. Response to warfarin is partially determined by polymorphysms in two genes (*VKORC1* and *CYP2C9*) resulting in the need for

dose variations between different patients (Wadelius et al., 2005). This explains, why, for example Afro-Americans are more resistant to warfarin, where as, American-Asians are more sensitive to it (Reider et al., 2005)

Its disadvantage relates to increased risk of some bleeding, with severe effects if not treated rapidly. The use of Warfarin must be monitored through INR-test to monitor therapeutic levels, ideally between (2.0- 3.0). Too high doses of warfarin would cause spontaneous bleeding. So at therapeutic levels, only PT/INR is affected.

Its indications are prophylaxis and other thromboembolic complications in cardiac valve replacement and atrial fibrillation

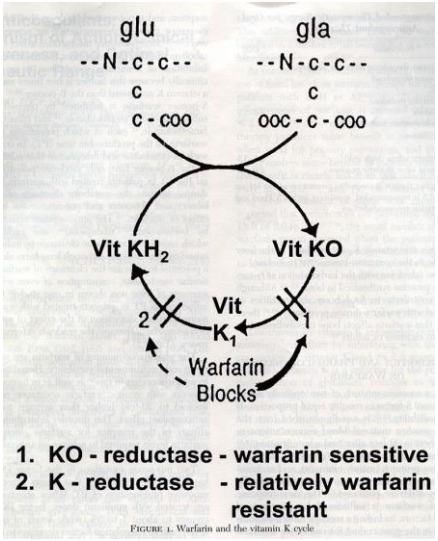


Figure 9. Vitamin K epoxide reductase enzyme that recycles oxidized vitamin K to its reduced form after carboxylation activity (Ansell et al., 2008)

Source: http://www.ashp.org/s_ashp/docs/files/r-aboutwarfarinpart1.pdf (Accessed 02.05.2015)

In addition to pharmacogenomics, different other factors affecting warfarin activity in the body may relate to age, albumin concentrations, liver dysfunction, diet with high levels of vitamin K, such as liver and green leafy vegetables, different disease states of liver and thyroid glands, and different drug interactions that may affect the metabolism of warfarin in the body. Life styles, including smoking, excessive drinking and exercise seem also to affect partial thrombin time as well.

http://www.ashp.org/s_ashp/docs/files/r-aboutwarfarinpart1.pdf (Accessed: 02.05.2015)

3.4 New Oral anticoagulants (NOACs) Dabigatran, Rivaroxaban and Apixaban

Dabigatran, Rivaroxaban, and Apixaban are new brands of oral anticoagulants (blood thinners) as alternatives to Warfarin. No blood tests for international normalized ratio (INR) monitoring are required while offering similar results in terms of efficacy (van Ryn et al.,2010; Eerenberg et al., 2011). Dabigatran is a direct thrombin inhibitor used to prevent stroke for patients suffering from atrial fibrillation, deep vein thrombosis, pulmonary embolism and other non-heart valvular conditions.It has a half-life of 12-14 hours with maximum anticoagulation effect within 2-3 hours after ingestion (http://www.drugs.com/pro/pradaxa.html)

Dabigatran etexilate is converted by serum esterase enzyme into Dabigatran. Its target is Factor IIa (free and clot-bound thrombin). Through direct inhibition of thrombin, it inhibits the development of a thrombus by blocking the conversion of fibrinogen into fibrin; Half-time about 14 days. Coagulation cascades for different NOACs are shown in appendix 12.

Approved indications for using Dabigatran:

Atrial fibrillations, Reducing risk for myocardial infarction and systemic embolism for patients with some risk factors including previous heart attacks, symptomatic heart failure, over 65 years old with diabetes or hypertension. Used also for reducing risk of VTE after knee or hip surgery. It is offered in 2 doses 110 and 150 mg capsules.

With respect to safety of using dabigatran vs warfarin, for the 150-mg dabigatran dose the annual rate of major bleeding was not different (3.11%; *P*=.31) compared with warfarin (3.36%) but was lower with the 110-mg dose (2.71%; *P*=.003). The rates of hemorrhagic stroke with the 110- and 150-mg dabigatran doses were lower than that with warfarin (0.12% and 0.10% vs 0.38%; *P*<.001).

Source: http://scienceindex.com/stories/3288541/Comparative_Effectiveness_of_Dabigatran_Rivaroxaban_Apixaban_and_Warfarin_in_the_Management_of_Patients_With_Nonvalvular_Atrial_Fibrillation.html (accessed 28.04.20149 ; and http://www.mayoclinicproceedings.org/article/S0025-6196(13)00222-X/fulltext#appsec1 (accessed 02.05.2015)

Both Rivaroxaban and Apixaban are direct Factor Xa inhibitors used in the primary prevention of VTE and the prevention of stroke and systemic embolism in patients with

nonvalvular AF. It is also used in the treatment of Pulmonary embolism and deep venous thrombosis and for reducing the risk of recurrent DVT and PE after initial treatment.. Its bioavailability is 50 %.

In 2 different studies, EINSTEIN and EINSTEIN-PE, the main safety outcome of major or clinically relevant non-major bleeding occurred at similar rates in both treatment arms. In the continued-treatment study, 4 patients taking rivaroxaban (0.7%) and no patients taking placebo had non-fatal major bleeding, which was not significant (Buller et al., 2012).

With respect to safety of rivaroxaban vs warfarin, there was no difference between patients taking rivaroxaban and those taking warfarin in terms of all bleeding events (14.9% vs 14.5% per 100 patient-years; *P*=.44) and major bleeding events (3.6% vs 3.4% per 100 patient-years; *P*=.58). Rates of intracranial hemorrhage and fatal bleeding were however, less with rivaroxaban therapy (0.4% vs 0.8%, *P*=.003 and 0.5% vs 0.7%, *P*=.02, respectively).

Source: http://www.mayoclinicproceedings.org/article/S0025-6196(13)00222-X/fulltext#appsec1

In the ROCKET- AF randomized double blinded study, rivaroxaban 20 mg, once a day dose was compared to daily adjusted dose of warfarin (INR 2.0- 3.0) using about 14 000 AF patients with non-valvular atrial fibrillation for the prevention of stroke and emboli, and the study concluded that rivaroxaban was just as effective as warfarin to prevent stroke and systemic emboli in the selected patients. In the rivaroxabn patients' group, there were fewer incidents of intracranial and fatal bleedings.

For Apixaban, rate of major bleeding per year was 1.4% compared with 1.2% with aspirin use in the AVERROES trial (*P*=.57) and 2.1% compared with 3.1% with using warfarin in the ARISTOTLE trial (*P*<.001).

Source: http://www.mayoclinicproceedings.org/article/S0025-6196(13)00222-X/fulltext#appsec1 (accessed 02.05.2015)

Comparative Properties of Warfarin, Dabigatran, Rivaroxaban, and Apixaban are given in appendix 13

3.5 INR-Testing and Monitoring

International Normalized Ratio is a standard monitoring measure for the time it takes for the blood to clot. It is also called prothrombin time. This is crucial for patients using anti-coagulants due to some thromboembolic disease, such as deep vein thrombosis or atrial fibrillation. It gives an indication of the available levels of clotting factors.

Management of warfarin therapy is a challenge since the pharmacodynamics response is delayed and often difficult to predict. The antithrombotic effect of warfarin manifests itself after about the fifth day of therapy, which is dependent on the clearance of prothrombin (Hirsh et al., 1999).

Both efficacy and safety of warfarin therapy depend on maintaining the patient's INR values within the target range for the disease indication. INR monitoring should be performed daily, once the patient is started on anticoagulation therapy until the INR is within the therapeutic range for at least 2 consecutive days. For the therapeutic monitoring of warfarin treatment to be successful, one need to both measures INR values correctly, and interprets the results properly to monitor and maintain optimal dosage of warfarin with respect to the patient's health state (Kearon, et al., 2008).

INR has a therapeutic range, ideally between 2-3 as shown in the figure 10 below.

It has no units. It is simply a ratio: INR = (PT Patient)/ PT Control ISI,

where ISI = international sensitivity index

The higher the INR value, the longer is clotting time, thus increasing potential risks of bleeding. The lower it is, the risk of developing a clot increases, as shown in figure 10 below.

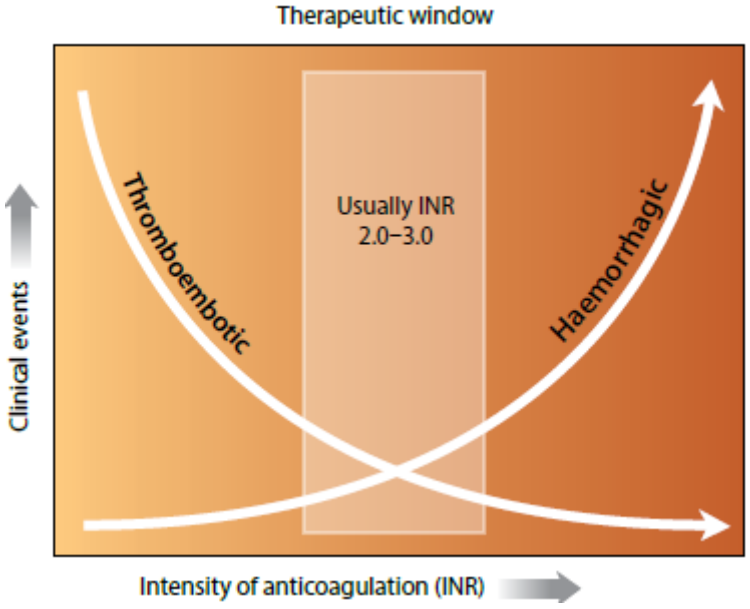


Figure 10. Graphical representation of the recommended INR therapeutic range for warfarin administration.

Source: (Blann, 2003)

http://www.bpac.org.nz/BT/2010/November/inr.aspx

The range of (2.0- 3.0) is recommended for the prophylaxis or treatment of venous thromboembolism and for the risk- reduction of systemic embolism for patients with valvular heart disease and atrial fibrillation. The target range may be as low as 1.5 for people over 75

due to the risk of intracranial bleeding. Recommended therapeutic range for oral anticoagulant therapy is given in appendix 14 (Hirsh et al., 1998)

The Common Pathway of blood- clot formation involves both an intrinsic pathway representing partial thromboplastin time (PTT), and an extrinsic pathway representing prothrombine time (PT) as shown in figure 11 below

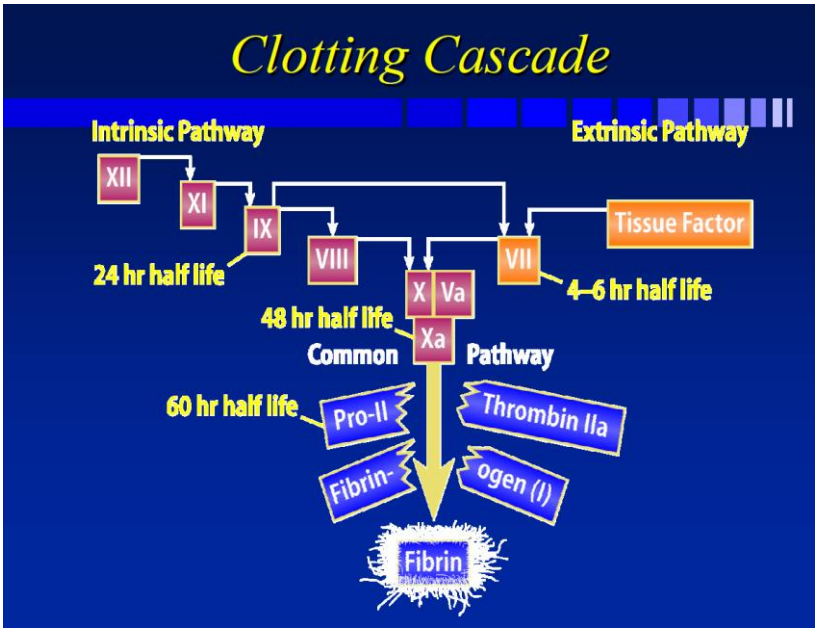


Figure 11. Blood clotting cascade showing both intrinsic and extrinsic pathways

Source: http://www.ashp.org/s_ashp/docs/files/r-aboutwarfarinpart1.pdf (accessed 30.04.2015)

Factor X is activated, either by VIIa or tenase , to form Xa – aka prothrombinase. Thrombin is factor IIa and it changes to prothrombin, as factor X is activated with calcium ions.

Factor V is not activated until it has come into contact with thrombin itself. Thrombin will then activate fibrinogen to fibrin. Fibrin strands will begin to join and cross-link together with the help of factor XIIIa.

XIII is also activated by thrombin, and functions as a fibrin stabilising factor.

http://almostadoctor.co.uk/content/systems/haematology/clotting/physiology-clotting

Coagulation process is therefore, monitored in the laboratory through measurement of prothrombine time (PT-INR), where – Plasma + Calcium + Tissue Thromboplastin

(TF) + factors VIIa → Xa + V → IIa → **CLOT**

Source: (http://www.ucdenver.edu/academics/colleges/medicalschool/departments/surgery/education/GrandRounds/Documents/GRpdfs/2007-2008/3-17-08%20Whitehill.pdf)

With over anti-coagulation, where INR value is 5-9, it is recommended that warfarin therapy stops for few days until normal range is achieved, and vitamin K 1.0 – 2.5 mg, is administered orally to help reducing INR value and reduce any risk of serious bleeding. If INR value is > 9, without bleeding, 2.5 – 5 mg vitamin K is recommended. If major bleeding occurs, it is recommended with 10 mg vitamin K, and transfer to secondary care for factor IV replacement.

Source: http://www.bpac.org.nz/BT/2010/November/inr.aspx

4 Literature Review

I performed a systematic literature review to get a general overview of thromboembolism disease, prevalence and outcomes of venous thromboembolism (VTE), atrial fibrillation (AF), stroke, and the different therapeutic practices of antithrombotic medicines, and how warfarin based treatment is monitored using INR testing.

Literature search was carried out over intermittent periods during the last 3 years (September 2011- April 2014) using different databases, including PubMed, Cochrane Library (reviews), Medline, The Lancet and the Norwegian Medical Associations Journal/ Tidskrift for Den norske legeforening. For Tidsskrift for den norske legeforening, the search was restricted to papers also published in English and the period 2008 to 2014. For all other journals, there was no time limit.

Different search terms were used including *venous thromboembolism, embolic thrombosis, atrial fibrillation, warfarin, INR and INR monitoring.*

Many thousands of articles were displayed reflecting the amount of ongoing research in this field. A brief scan of few selected articles was made, based on title and relevance. Results of this search are displayed in the table below:

Table 1. Literature search results from different databases, based on disease manifestation and INR testing and monitoring.

	VTE	DVT	Atrial fibrillation	Pulmonary embolism	Warfarin	INR Testing	INR Monitoring
PubMed	**15848**	**66779**	**49239**	**42291**	**21136**	**569**	**1535**
Cochrane Library Reviews	**169**	**307**	**198**	**360**	**261**	**115**	**78**
Medline	**1575**	**3788**	**27147**	**30684**	**12953**	**185**	**541**
The Lancet	**102**	**132**	**889**	**862**	**664**	**57**	**84**
Tidsskrift for Den norske legeforening	**8**	**12**	**126**	**57**	**256**	**25**	**28**

The low display search result in *Tidsskriftet for Den norske legeforening* is probably due to limiting the search to 5 years (2008-2014) and for articles published in English.

In addition to the many international studies, I referred to in my description of the different manifestations of thromboembolism in the background section of this thesis, which related directly to Warfarin therapy, its monitoring and side-effects for treatments of thromboembolism and atrial fibrillation, for costs and patients visits estimates, I will focus on reviewing a Health Technology Assessment report produced by Martin Connock and his colleagues (Connock et al., 2007) for the *National Health Services (NHS R&D HTA Program, October 2007)* and 2 different reports produced by the Norwegian Knowledge Centre for Health Services (Kunnskapssenteret) in 2010 and 2013. I will also use data given in a short *report that* Professor Ivar Sønbø Kristiansen and myself produced collaboratively in 2010, and some other recent reports from the Norwegian Medicines Agency (NoMA/ Legemiddelverket).

Connock and colleagues examined clinical effectiveness and cost effectiveness of different management's strategies of oral anticoagulation treatment, including self-management. 16 randomized trials were included. 2 trials included patients with AF only; three trials included patients with mechanical heart valves, and the rest with mixed indications for long-term anticoagulation therapy. They concluded that there

was no significant difference in monitoring the target therapeutic clotting range between self-administered and family doctor's procedure.

I used this article to examine possible additional research questions for my own study where therapeutic self-management was an alternative. In their findings, patient self-management was more expensive than standard NHS management (£ 417 vs £ 122 per patient year), hence this option was not realistic.

In their method evaluation report *(Metodevurdering rapport nr 22-2010),* the authors conducted different literature studies, including 4 systematic reviews of 14 (average-good quality) randomized controlled trials to evaluate clinical efficacy of primary intravenous thrombolytic treatment for acute stroke, within 5 hours of developing symptoms compared to treatment without thrombolysis. They also evaluated different therapies for the secondary prevention of stroke including anticoagulation therapy by comparing warfarin with aspirin (acetylsalysic acid/ ASA) for prophylaxis of stroke, for patients suffering from atrial fibrillation. 2 different antiplatelet therapies were also examined where ASA was combined with slow-release dipyridamole as compared to using ASA on its own, and the second antiplatelet therapy compared ASA + dipyridamole with clopidogrel monotherapy. The authors used Markov-modelling to evaluate treatment costs and QALYs with different treatment strategies and life-time costs associated with stroke. Both genders were analyzed at 50 and 70 years also, and were followed until death. Different sensitivity analysis was also performed. I will focus my review on the thrombolytic therapy only, since it is most relevant.

Studies of this report conclude that disability was reduced when thrombolytic treatment is administered within 3 hours of stroke onset, compared to no thrombolytic therapy. (RR 0.75 and confidence interval 95% 0.64-0.89). There was no difference in either treatment strategies with respect to mortality (RR 0.87, 95 % confidence interval 1.18-0.75). Warfarin was found to reduce risk of recurrent stroke in atrial fibrillation patients compared to ASA alone. Warfarin was also found to increase bleeding events in patients compared to ASA alone (RR 2.80, 95% confidence interval 1.70-4.80). Thrombolysis within 3 hours resulted in 0.24 QALYs loss compared to no thrombolytic treatment, and it reduced costs with a cost-effectiveness ratio of NOK 665 000 per QALY gained (Rapport fra Kunnskapssenteret 22/2010) ; (Wisløff et al., 2010).

In their *HTA report No 5-2013*, the authors performed different cost- effectiveness analysis of the new oral anticoagulants Dabigatran, Rivaroxaban and Apixaban (ONACs) relative to each other and to Warfarin with respect to prevention of stroke in atrial fibrillation patients. Different risk-levels were developed using Markov modelling where assumptions relating to bleeding, stroke and myocardial infarction for atrial fibrillation patients were increased. They used Scandinavian registries for estimating different risks of events. Norwegian fees were used in estimating costs..

The authors estimated also the lifetime costs and effects in terms of net health benefit of new oral anticoagulants compared to warfarin when CHA2DS2-VASc =1 and the expected remaining QALYs for a 65 year old patient suffering from AF, with a medium risk of stroke is *13 QALYs* (discounted: 9.12 QALYs) when treated with warfarin.

The incremental net health benefit (discounted) *for Dabigatran 150, was 0.15*, for Dabigatran 110, was -0.04, for *Rivaroxaban 0.08*, and for *Apixaban was 0.11*.

A general conclusion was that all three NOACs increased remaining quality-adjusted life expectancy, but total costs of using them were also increased. All three NOACs were likely to be cost-effective compared to warfarin, and produced significant reductions in intracranial bleedings as well when compared to warfarin (at 5 % CI, $P<0.05$). For high risk patients, Dabigatran seemed to be the most cost-effective. Results were, however, inconclusive with regards to cost-effectiveness due to many uncertainties in their model.

Their cost utility analysis costs were expressed in NKR and outcomes in QALYs from a health care perspective. Costs and effects were discounted at a discount rate of 4%. Probability assumptions for both ischemic stroke and bleeding were based on a Swedish registry, and the mean follow-up time was 1.5 years. In estimating their costs, both costs and effects were assumed to last until death. Three different doses of Dabigatran were used (110 mg, 150 ESC and 150NoMA); 5 mg for warfarin, 20 mg for Rivaroxaban and 5mg for Apixaban.

The authors also assumed that patients using NOACs had *4.17* GP /private specialist visits per year. NoMA assumed *5* patient-visits.

They recommend further large scale randomized control trials, in different countries, for different patients' selects in order to reduce their decision uncertainty (HTA Rapport fra Kunnskapssenteret No5-2013).

In their two reports regarding reimbursement applications for Dabigatran (Pradaxa), dated 22.05.2012, and for Rivaroksaban (Xarelto), dated 22.11.2012, The Norwegian Medicines Agency (NoMA) assessed the suitability of these two new oral anticoagulants (NOACs) with respect to blue- prescription form authorization . NoMA is the official Norwegian administrative body covering pharmaceuticals and their approval. The drugs reimbursement scheme discussed descriptions of Dabigatran and Rivaroxaban, their treatment regimes, costs, clinical benefits with respect to relevant illnesses and epidemiology, and they positioned the two NOACs in the existing treatment programs and relevant alternatives. Side effects over long-term use were evaluated as well. NoMA also reviewed, different dosages presented and their pricing, and evaluated the different defined studies and their pharmacoeconomic analyses performed with respect to their budgetary consequences as well.

The reimbursement application for Dabigatran was assessed only for the treatment/ prevention of stroke and systemic emboli (SEE) for atrial fibrillation patients .(Refusjonsrapport Dabigatran. NoMA, 22.05.2012)

http://www.legemiddelverket.no/Blaa_resept_og_pris/Helseoekonomiske%20rapporter/Documents/2012-2011/Pradaxa_atrieflimmer_2012.pdf

The report describes a prospective, randomized large-scale RE-LY study where either Dabigatran 110mg or 150mg (blind studies) were compared with adjusted dose warfarin (INR 2.0-3.0) (open) study involving18000 patients over 2 years. Specified *excluding* criteria related to patients with added risks and valvular atrial fibrillation.

Reported findings indicated that Dabigatran (150mg) was better than Warfarin in preventing stroke and systemic emboli for same-risk patients for bleeding. Dabigatran (110mg) had similar effect to Warfarin.

In their application, Boeringer-Ingelheim Pharma KG presented an 8000 (NOK) saved (reduction) costs with respect to INR control per patient when using Dabigatran instead of Warfarin. This was reduced to (3300) NOK. Other adjustments for life-quality were included, and Dabigatran was estimated to have 22 000 (NOK) savings

and 0.22 QALYs per patient per survival time compared to Warfarin, and both costs and QALYs were discounted at 4% per year. Other cost effectiveness studies for ASA and for treatment/ prevention of thromboembolic disease with planned hip and knee replacements were referred to as well.

Drop-rate from this study due to clinical events were 4,4% for Dabigatran 110mg, 4,1% for Dabigatran 150mg and 3,0 % for Warfarin (Sorensen et al., 2011)

Table 2. Intention to treat (ITT) analysis of primary end point- first episode of stroke or systemic emboli for patients using Dabigatran110 mg, Dabigatran 150 mg and Warfarin.

(12) Dabigatran 110 mg x 2	**Dabigatran 150 mg x 2**		**Warfarin**
Patients (randomized)	6015	6076	6022
Stroke or systemic emboli			
Episode(%)[1]	183 (1.54)	134 (1.11)	202 (1.71)
Hazard ratio over warfarin (95% CI)	0.90 (0.74, 1.10)		0.65 (0.52, 0.81)
p verdi superiority p verdi non-inferiority	p = 0.2943 p<0.0001		p = 0.0001 p<0.0001

Source:
http://www.legemiddelverket.no/Blaa_resept_og_pris/Helseoekonomiske%20rapporter/Documents/2012-2011/Pradaxa_atrieflimmer_2012.pdf

Rivaroxaban had approved indications for use in the prevention of venous thromboembolism (VTE) for patients undergoing elective hip or knee surgery, recurrence of VDT and lung emboli episodes in adult patients.

Reimbursement application for Rivaroksaban was evaluated for the prevention of stroke and systemic emboli for atrial fibrillation patients (Refusjonsrapport Rivaroksaban, NoMA, 22.11.2012)

The ROCKET AF-study was described. The study performed was a prospective, randomized double-blinded study of the efficacy of 20mg daily doses of Rivaroxaban in comparison with adjusted dose Warfarin (INR 2.0-3.0) for 14000 patients with non-valvular atrial fibrillation. Economic analysis included comparisons of Rivaroxaban with Warfarin and Dabigatran as well. Findings showed that Rivaroxaban was just as

effective as Warfarin, with significantly lower incidents of intracranial and fatal bleeding episodes in the Rivaroxaban test group . In the quality adjusted life years analysis, Rivaroxaban was shown to be cost effective with 231 824 (NOK), and similar data analysis for the «safety-on-treatment" group gave cost effective value of 127 298 (NOK). Discount rates of 4% were used. Medicinal costs for Rivaroxaban were much higher than for Warfarin. There were some uncertainties with respect to the compliance evaluation of Rivaroxaban , and the quality of warfarin therapy given in the ROCKET AF study compared to the standard clinical practice.

Table 3. Analysis of safety end- points, incidents of intracranial bleedings and fatality for Xarelto and Warfarin

	Xarelto 20mg daily dose 15mg for patients with reduced kidney function	**Warfarin** Therapeutic interval INR (2.0-3.0)	**Hasardratio** (95 % KI) p-verdi
Intracranial bleeding	55 (0,49)	84 (0,74)	0,67 (0,47–0,93) p=0,019
Mortality	208 (1,87)	250 (2,21)	0,85 (0,70–1,02) p=0,073

Source: http://www.legemiddelverket.no/Blaa_resept_og_pris/Helseoekonomiske%20rapporter/Documents/2012-2011/Xarelto_atrieflimmer_2012.pdf

4.1 Research Questions

After reviewing the above literature, and other relevant studies, and based on the raw-INR data at hand for 2009, 2010 and 2011, and NOACs data obtained from the Norwegian medicines agency, the following research questions were set in this study:

a) What was the number of INR-tests taken in Norway in 2009 in different laboratories, and what were their societal costs ?
b) How do the numbers of INR-tests at GPs' or private specialists' clinics vary between 2009 -2011?
c) What is the trend of oral anticoagulants use for the years 2009- 2014 ?

d) What were the reduced INR visit-numbers and the reduced total costs for patients with atrial fibrillation as a main diagnosis for 2009, 2010 and 2011?

e) Would reduced GPs visits for atrial fibrillation patients have any impact on the cost- effectiveness of NOACs compared to Warfarin when evaluating their incremental net health benefit ?

f) What were the total use-cost for the new oral anticoagulants (OANC) Dabigatran, Rivaroxaban and Apixaban in 2013 compared to use-costs for Warfarin in 2013 ?

g) What were the 2013 reduced- visit costs for Dabigatran ?

5 Methods

The method section discusses the different types of empirical data gathering tools and techniques used for this study. According to Myers and Avison (2004, p.5) a research method is a "strategy of enquiry which moves from the underlying philosophical assumptions to research design and data collection".

5.1 Case study

Different sets of empirical data for the 3 different sections in this thesis were collected differently.

A case study is an empirical research inquiry method used when an" in-depth holistic investigation" is utilized to study a contemporary phenomenon within its real-life context (Feagin, Orum, & Sjoberg, 1991), especially when the "boundaries between phenomenon and its context" are not clearly defined (Yin, 1981). The case study inquiry usually relies on multiple sources of evidence allowing for triangulation approach when dealing with methodologies and data sources (Yin, 1984) and (Denzin, 1984).

In addition to being used for early exploration of research theme, case studies may also be used for descriptive or explanatory purposes as well, in order to describe a specific situation, such as a case history, or to test explanations for why specific events have occurred by adopting causal inferences (Stake, 1995). A descriptive theory better be developed before starting a project where either single case or multiple case applications are used (Pyecha,

1988). This facilitates maximizing learning effect in the short period of time available for conducting a study and guides data collection processes and data analysis especially when there are many more variables of interest than data indicates. This contrasts case study research with grounded theory, for example, where a theory is usually developed during / after research investigations is over (Yin, 1994; 2003).

5.2 Survey

Surveys are widely used methods for data collection. The mode may be telephone and face-to-face interviews or through mail/ email. Sets of questions are usually set beforehand, and a sampling strategy is established. Data collection is performed and monitored, and reminders are often sent to encourage response from non-responders. Collected data is compiled and entered into a data-base, for processing and later analysis. Outcome may be investigative and/or exploratory. The aim of survey research is not to describe the individual sample, but analyze the larger data-set collected. A common error that occurs is selection bias. When two variables are correlated, we are able to make predictions for these two variables, in our case, number of INR-tests performed and their cost to the national health system (Straus A & Corbin J, 1998).

Reliability of collected data relates to its consistency, whilst validity reflects whether we are measuring what we want to measure. Internal validity relates to our selected sample and external validity reflects the extent to which we are able to extend our findings to much larger populations (Ragin C. C, 1999); (Weisberg H.F, 2005)

Source: http://intqhc.oxfordjournals.org/content/14/4/329.full

5.3 Section1 study- methodology

Data collection here was done in collaboration with Professor Ivar Sønbø Kristiansen at the Department of Health Management and Health Economics at UiO

To get an estimate of the INR-test numbers performed at different Norwegian hospitals, we focused our attention on the hospitals located in the South-East Health Region (SØ-HF), which is one of four regional health enterprises, established in June 2007. The South East Health Region comprises 11 different health enterprises with a catchment population of *2,262,951* out of a total *4,799,252* (SSB, 2009). Assuming homogeneity of INR-test

application throughout different regions in Norway, an account of the INR-tests performed in may be indicative of total INR-test costs nationally.

A search of the South East Regional Health Enterprise's (SØ-HF) website was performed and a list of all hospital laboratories performing INR testing was compiled (Table 1). Visits to each and every hospital's website were also undertaken and key contact personnel in each laboratory were identified, and their email addresses were registered. Wherever specific lab leaders/ head bioengineers were listed, an e-mail was sent to them, in the form of a short survey. We outlined the type and purpose of this study and requested them to supply us with the numbers of INR tests performed at their laboratory in 2009, preferably divided into inpatients, internal outpatients (tests on patients visiting the hospital's outpatient clinic (in Norwegian: poliklinikk") and external outpatients (test performed on blood samples sent from GPs or other physicians). Deviations from these INR test subdivisions were specified in the added comments column of the results table.

Some laboratories had no specific contact e-mail, and we sent an email to the hospitals «post mottak" or similar. Here, we sent a brief e-mail asking for names and emails of lab leaders/ head bioengineers for further contact. Upon receiving such information, similar e-mails were sent to them requesting numbers of INR tests performed in their lab in 2009, as mentioned above.

Reminder e-mails and subsequent telephone contact were undertaken after a period of 10 days requesting non-responder labs for INR test numbers.

5.4 Section 2 study- methodology

Data collection here was done in collaboration with Professor Ivar Sønbø Kristiansen at the Department of Health Management and Health Economics at UiO,

To get an estimate of the unit costs and total costs associated with performing the tests in different contexts, the same approach for data collection was uses as for section 1. In addition, internet searches, and contacts with employees in the Directorate of Health, in the Regional Health administrations and various other people in health care related departments.

INR tests are analyzed in a variety of laboratories: In hospitals, in GPs' and private specialists' on-site laboratories, in nursing homes and in commercial laboratories.

5.5 Section 3 study- methodology

In collaboration with Associate Professor Torbjørn Wisløff at the Department of Health Management and Health Economics at UiO, relevant data here was extracted from the original raw data used in the previous two sections accounting for numbers of INR-test related contacts between INR patients and their GP/ private specialist for the years 2009, 2010 and 2011.

Use-cost data/ Prescriptions- data was extracted from the Norwegian Prescription Database (NorPD)/ Reseptregisteret for the period 2009-2014. For dispensed drugs in Norway. One may search for data about the users of a particular drug or drug category. The data may be split by sex, age and geography.

Selected search criteria:
Drug:

- B01AF02 Apixaban
- B01AF01Rivaroxaban
- B01AE07 Dabigatran etexilate
- B01AA03 Warfarin

Period: 2014, 2013, 2012, 2011, 2010, 2009
Age: All ages
Residence: Entire country

Gender: the numbers in the report are for Both sexes

Source: Norwegian Prescription Database (NorPD/ Reseptregisteret, (20.05.2014)

http://www.norpd.no/Prevalens.aspx

6 Data Description

Here I give an account of the different data used in this study and the basis of using different numbers for cost calculations.

6.1 Raw Data

Three sets of raw HELFO data were obtained from a senior advisor in health economics and financing at Norwegian Directorate of Health in September 2013. This data displays numbers of patients with any medical disease diagnosis who had an INR test taken at GP or private specialist's clinic, the number of patient visits according to diagnosis groups, gender and age-groups in Norway for the years 2009, 2010 and 2011. Where multiple diseases are present, the patient's main diagnosis is used to account for the total numbers of INR-tests performed per year. So, the data displays the number of visits and the number of patients with "710 takst" according to diagnosis, age groups and sex. "takst 710" is a code for INR-test ", and code (K 78) is for INR-tests for patients with atrial flimmer is the main diagnosis.

6.2 Diagnosis Code- Categories of the raw data

Diagnosis categories displayed in the data, most probably combines both, the International Classification of Primary Care coding (ICPC-2) and the ICD-10 coding systems.

In health care, different standardized diagnosis codes are used to classify and identify different diseases and symptoms that form the basis for patient encounters. They are also used as decision support systems and for reimbursements. Such codes are often used parallel to intervention and procedure codes. Examples of such codes are ICD-10 Procedure Coding System, which describes the International Statistical Classification of Diseases and Related Health problems and it is maintained by the World Health organization (WHO, ICD. 2011). Another coding system is the ICPC-2 (International Classification of primary care), which is an alphabetical index that describes different encounters, reasons , episodes and interventions offered at primary health care, thus allowing for episode-related data structuring (WHO, ICPC-2. 2011); (KITH, 2014).

Coding systems are often revised, reflecting new and developing advances in medical treatments and health care interventions (Wikepedia, 02.06.2014), (Steindel. S, 2010).

Statistical classification groups together different medical conditions and concepts into categories such as pharmaceutical, and diagnostic codes. It also allows for including unspecified medical conditions as residual categories. Weaknesses of coding systems is that it

restricts medical decisions to an "hierarchical tree structures" without taking much account of parallel branching that might disturb main disease related focus. Interconnectivity and communication between different codes is not always appropriate either (Cheng et al., 2013). Health personnel might develop a "usability bias" depending on their preferential and familiarity issues associated with using only one specific coding system over many years

Coding systems used in the raw data probably combines codes from both the ICPC-2 and the ICD-10 systems. I cannot justify for the *C, G, I, J, L and M* codes in the ICPC-2 coding-table. I therefore referred to them as ICD-10 codes, with relevant disease association.

These represent only a small number of INR-test visits, so their actual significance on total visit-count is minimal, I would assume, even though no statistical significance testing was performed.

Selection statistics from the Norwegian Prescription Database (Reseptregisteret) use a drug selection based on either drug categories or the Anatomical Therapeutic Chemical classification system (ATC) Different levels may be selected in a tree-structure.

A list of disease categories is presented in Appendices 4a and 4b.

7 Data- calculations of Numbers and Costs

In this section, I will perform different calculations of numbers and costs for the three different sections of this study, as mentioned earlier.

7.1 Section 1 study: Numbers of INR- tests performed in 2009

Data used here is the INR-test data that was collected in 2010, as it appears in the "Report of 26th May 2010: Use of INR Tests in South-East health Region, Norway 2009". Ref: (Murad, H. & Kristiansen I. S, .2010).

The number of hospital laboratories performing INR-tests in South-East Regional Health Enterprise, Norway 2009 is given in (Appendix 2 and 3)

- Laboratories marked in red did not respond to the data request
- Number of INR tests accounted for represented the county of Østfold, with a population of *268 584* inhabitants in 2009, representing *1740* tests per *10 000* populations

- Assuming homogeneity amongst different INR test guidelines and practices in Norwegian hospitals, and that Østfold county is representative for the whole Norwegian population, we got an estimate for the total INR tests performed in Norway in 2009

Assumptions made: Norwegian population in 2009 = *4799 252 inhabitants*

Number of INR-tests performed in hospitals in 2009= *835, 202 tests*

Adjusted numbers of INR-tests performed in hospitals in 2009 = *949,091tests*

This number does not include INR-tests performed at GPs/ private specialist's laboratories, or private chemistry laboratories or nursing homes.

Number of INR-tests performed in 2009 included *250,795* as in-patients, *76,856* internal out-patients (patients treated at the hospitals' outpatient clinics), and *62,623* as external out-patients (patients treated by GPs, private specialists, and in nursing homes (Murad & Kristiansen 2010). Some laboratories only reported the total number of test without specifying for which group of patients they were taken

All hospitals in the county of Østfold, responded to our survey, so data obtained represented all hospital laboratories there. The total number for performed INR-tests was *46,741* in a population of *268,584* as of January 2009 *(*www.ssb.no).

This represents *1740* tests per *10,000* populations. Assuming the INR-tests number in the county of Østfold is representative for the whole Norwegian population of *4,799,252*, the estimated total number of INR tests performed in hospital laboratories during 2009 was *835,202.* Assuming that the South-East Health Region comprises 47% of the total Norwegian population, the Norwegian hospitals total estimate in 2009 would be *949,091*. This is a conservative estimate.

Source: (Kristiansen I.S, report of 30.07.2010)

To estimate Total numbers of INR-tests carried in Norway in 2009, the same INR-test data was used, which was collected in 2010, as it appears in the "Report of 30th July 2010: Societal Costs of INR Testing in Norway 2009", with permission.

Ref: (Kristiansen I.S, report of 30.07.2010).

Numbers for INR tests from GPs and private specialists was obtained from The Norwegian Health Economics Administration (HELFO), for commercial labs, numbers were obtained

from Fürst Medisinsk Laboratorium and Unilab/Capo. Other labs comprise Volvat Medisinske Senter, Feiringklinikken, and others. We have no direct data from them. Our estimate is 10000 tests.

Our estimate for the total numbers of INRtests performed in Norway in 2009 *was 1 783 202*, tests as shown in the table below.

Table 4. Number of INR tests according to patients and laboratory type in Norway, 2009

	Hospital in-patients	Hospital out-patients	Other out-patients	Total
Hospital laboratories	536 711	164 475	134 016	835 202
GPs and private specialists			902 200	902 200
Commercial laboratories			35 800	35 800
Other laboratories	5 000		5 000	10 000
Total	541 711	164 475	1 077 016	1 783 202

Source: (Kristiansen I.S, report of 30.07.2010). With permission

7.1.1 Section 1 study: Social Costs of INR- tests performed in 2009

The costs associated with **section 1** of this thesis are related to the total numbers of INR tests and the different types of societal costs involved. Source: (Kristiansen I.S, report of 30.07.2010). With permission.

The type of costs included here are:

Doctors consultation, taking blood sample, analysis of blood sample, patient's travel costs, loss of productivity, if employed, and loss of leisure if not employed.

Cost units

- Cost of a doctor's consultation was based on consultation fee (229 NOK), number of warfarin users from Reseptregisteret for 2009 (86, 278 users), anticipated number of GP visits for other reasons than having INR test (5 visits per year). This gives 430 000 consultations for other reasons than INR testing. From our previous calculations, about 1,24 million outpatients tests were performed (1 783 202 - 541 711 = 1 241 491 tests. This means that about 800 000

outpatient- visits were taken specifically for INR monitoring. For these outpatient visits, we included the consultation cost, travel costs and patient-time costs.

- Cost of taking blood sample and sending it to lab : NOK 47.00 (Normaltariff takst 710a / Anon, 2009)
- Cost of the performing the INR test

  This is a complex estimate involving reimbursement schemes for different patients and hospitals. Fee code 710a for outpatients per test (NOK 4.00). 30% of total cost is covered by HELFO fees, therefore NOK13.33 fee was applied for all tests performed in hospital (902 000 tests.) . GPs get NOK 69.00 for on-site blood analysis and applies to all GP tests reimbursed by HELFO (902 000).

  Fürst Medisinsk Laboratorium received NOK 4.00 from HELFO and it was included in the 35,800 tests reported by Fürst for 2009.
- For other labs (10 000 test) we used NOK69.00, since the unit costs are probably high compared to volume of tests performed.
- Cost of informing patients about INR results, we used NOK 50 (Normaltakst 1bd) (134000+ 37000)
- Travel costs, NOK 50 (800 000 visits)
- Productivity losses and time costs for patients, In 2009, "the average income in Norway NOK437 400, or NOK327 per hour assuming 1870 working hours per year (http://www.ssb.no/emner/historisk_statistikk/ aarbok/ht-0901-lonn.html). Adding the social cost of labor, the value of one hour lost production can be estimated at NOK 327 per hour, or NOK 490.50 when using the 75% estimate. This amount was applied for the 800 000 visits that presumably takes place for solely having a INR test taken"

  Source: (Kristiansen I.S, report of 30.07.2010). With permission.

Total societal costs were therefor estimated at *NOK 705 mill in 2009*, which are considerable compared to the direct costs of the INR test itself, which were about NOK 70 mill. as outlined in table 5 below,

Table 5. Different costs of INR-testing according to cost category in Norway- 2009

Cost item	Number	Unit cost (NOK)	Total
Consultation fees for visiting a GP or other outpatient service	800 000	229,00	183 200 000
Drawing and sending blood sample	171 000	47,00	8 037 000
Cost of hospital INR testing	835 000	13,33	11 133 333
Cost of GPs' INR testing	902 000	67,00	60 434 000
Cost of commercial laboratory testing	35 800	13,33	477 333
Cost of other testing	10 000	69,00	690 000
Cost of informing patients	171 000	50,00	8 550 000
Patients' travel cost	800 000	50,00	40 000 000
Patients' time cost	800 000	490,50	392 400 000
Total costs			**704 921 667**

Source: (Kristiansen I.S, report of 30.07.2010). With permission.

7.2 Section 2 study: Numbers of INR- tests performed by GPs/ private specialists in 2009, 2010 and 2011

Here I will extract from the raw data available, the total numbers of INR- tests, performed by different GPs and Private specialists in the years 2009, 2010 and 2011, and the specific INR-tests where AF was the main diagnosis for the same period, for both males and females.

The number of INR-tests in the raw data 2009-2011 is displayed according to "takst 710" code, distributed over many diagnosis types, based on one major disease diagnosis, for simplicity. Code *(K78)* relates to INR-tests for patients with AF as a main diagnosis.

A reimbursement bill from a doctor coded "takst 710" for two diagnoses would therefore count only once, based on the principal diagnosis. Age groups were grouped into different categories, A 0-4 years), B (5-9 years), and so on. Group "Q" is coded for 80 tear old patients and over. Sex of patients is coded 1 for men and 2 for women, and 9 for undisclosed gender. This gender- code 9 was not included in collected data especially that such patients' numbers were extremely few compared to the total number of INR- GPs- visits.

So, the data displays the number of visits for patients with "710 takst" according to diagnosis, age groups and sex. (Appendix 3d, Table 3.3) and (Appendix 3e, Table 3.4). Data relating to atrial fibrillation patients (K78) was of most interest.

Age grouping was not used, as only differences in the number of INR-tests performed for different sexes was of any interest to us in this study.

Table 6. Number of INR- tests taken at GPs/ private specialists clinics for the years 2009, 2010 and 2011.

Year	Gender	Number of INR-tests, all ages, where AF is the main diagnosis	Total numbers of INR-tests per gender	Total numbers of INR-tests performed for both sexes
2009	Female	156315	388141	928 955
	Male	221747	540814	
2010	Female	165212	407262	979 059
	Male	234646	571797	
2011	Female	183871	436584	1 049 002
	Male	260299	612418	

HELFO data

7.3 Section 3 study: Numbers of users of Warfarin and NOACs for the years (2009-2014)

The numbers of users of Warfarin and the NOACs for this part of my study is extracted from the Norwegian Prescription Database (Reseptregisteret). Since the numbers of NOACs users was quite small until the year 2012, I have selected these numbers, per sex, only for the years 2013 and 2014, as shown in table 9 below.

Table 7. The numbers of users of warfarin per gender, and the total number of users for the years (2009- 2014)

				Total Warfarin users
Warfarin (B01AA03)	**2009**	**Female**	**34 605**	86 318
		Male	51 713	
	2010	Female	35 487	88 630
		Male	53 143	
	2011	female	36 809	92 131
		Male	55 322	
	2012	Female	37 989	94 709
		Male	56 720	
	2013	Female	35 191	87 994
		Male	52 803	
	2014	Female	31 041	77 750
		Male	46 709	

Reseptregister data: 2015

Table 8. Numbers of NOACs users, all ages, both sexes for the years (2009 – 2014)

	Number of users					
oral Anticoagulants	2009	2010	2011	2012	2013	2014
Dabigatran Etexilate	9	187	1168	4102	13879	15 357
Rivaroxaban	45	191	898	1332	13423	20 792
Apixaban	0	0	0	335	2260	8 640
Total NOACs users	54	378	2037	5434	29562	45189

Reseptregister data: 2015

Table 9. Numbers of NOACs users, all ages, divided according to gender and total users for the years 2013 and 2014

NOACs	Year	gender	NOACs users pr gender	Total NOACs users
Dabigatran	2013	Female	5 591	
		Male	8 288	13 879
	2014	Female	6 028	
		Male	9 329	15 357
Rivaroxaban	2013	Female	6 073	
		Male	7 350	13 423
	2014	Female	9 208	
		Male	11 584	20 792
Apixaban	2013	Female	1 222	
		Male	1 038	2 260
	2014	Female	4 097	
		Male	4 543	8 640

Table 10. Percentages of females using Warfarin for the years (2009- 2014), and females using NOACs for the years 2013 and 2014

	Males	Females	Percentage Females using Warfarin	Percentage females using NOACs
2009	51 713	34 605	40,1 %	
2010	53 143	35 487	40,0 %	
2011	55 322	36 809	40,0 %	
2012	56 720	37 989	40,1 %	
2013	52 803	35 191	40,0 %	43,6 %
2014	46 709	31 041	39,9 %	43,2 %

Reseptregister data.

7.3.1 Section 3 study: Predicted Numbers of users from linear regression for Warfarin usage (2004-2014) and NOACs usage (2009-2014)

Using prescription data for warfarin usage (2004-2009) a simple linear regression was made to predict the number of users of oral anti coagulants per 1000.

Table 11. Predicted number of warfarin users and NOACs from linear regression for the period (2004- 2014)

	Predicted number of users pr 1000 from linear regression	Warfarin	NOACs	Total Oral Anticoagulants (Warfarin+ NOACs) users per 1000
0	19,3417	19,15	,	19,15
1	19,7975	19,85	,	19,85
2	20,2533	20,38	,	20,38
3	20,7091	20,88	,	20,88
4	21,165	21,17	,	21,17
5	21,6208	21,45	,	21,45
6	22,0766	21,75	,1	21,85
7	22,5324	22,31	,4	22,71
8	22,9883	22,53	1,2	23,74
9	23,4441	20,69	6,5	27,20
10	23,8999	18,08	9,9	27,98

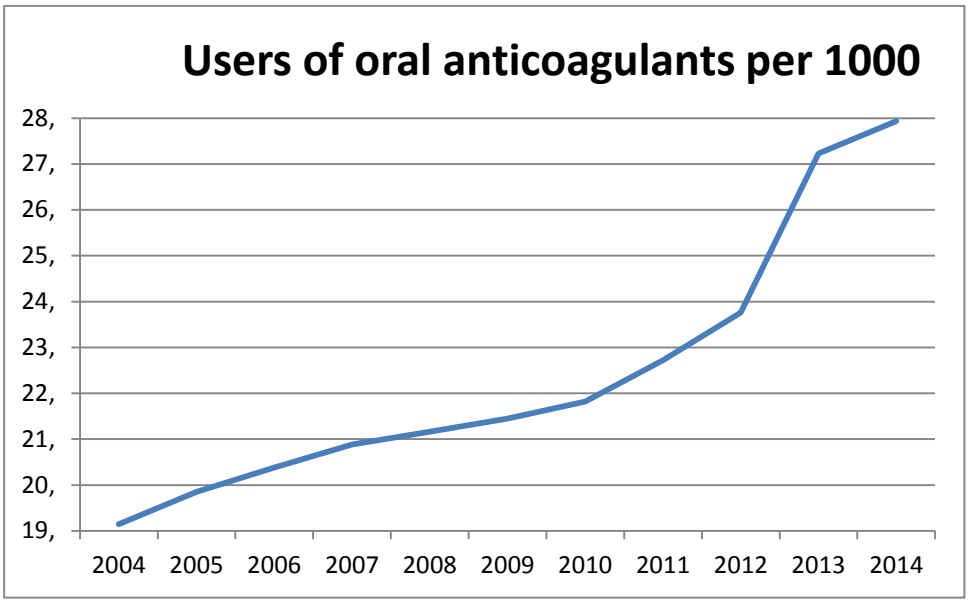


Figure 12. Total users of Oral anticoagulants per 1000 between (2004- 2014)

7.4 Section 3 study: estimated reduction of INR related visits to GPs/ private specialists for the years (2009-2011)

Based on HELFO-data for the years (2009-2011), we estimated total number of INR-test and number of INR-tests among those with atrial fibrillation as a primary diagnosis for male and female. Number of warfarin users was taken from the Norwegian prescription registry. By dividing number of INR tests by number of warfarin users, we get estimates of number of INR tests per warfarin users. If we assume that only those visits with atrial fibrillation as a primary diagnosis could be eliminated due to introduction of NOACs, and that patients with atrial fibrillation would have at least one GP visit with atrial fibrillation as primary diagnosis, estimated reduction in visits due to the introduction of NOACs would be between 3,3 and 4,0 as seen in table 12 below

Table 12. Estimated reduction in GPs/ private specialists INR-visits for males and females for the years (2009-2011)

Year	Gender	Number of INR-tests, all ages, where AF is the main diagnosis	Number of INR-tests pr warfarin user where AF is the main diagnosis	Total numbers of INR-tests	Total numbers of INR-tests pr warfarin user	Number of INR-tester without AF as main diagnosis.)	Estimated reduction in visits.
2009	Female	156315	4,5	388141	11,21633	6,7	3,5
	Male	221747	4,3	540814	10,45799	6,2	3,3
2010	Female	165212	4,7	407262	11,47637	6,8	3,7
	Male	234646	4,4	571797	10,75959	6,3	3,4
2011	Female	183871	5,0	436584	11,86079	6,9	4,0
	Male	260299	4,7	612418	11,07006	6,4	3,7

HELFO data

- The numbers of INR-tests pr warfarin user increases from 2009- 2011, regardless of gender.
- Number of INR-tests pr warfarin user where AF is main diagnosis = (Number of INR-tests/ Number of users of warfarin)
- Total number of INR-tests (without AF as the main diagnosis) = (Total numbers of INR tests/ Total number of registered warfarin users)
- Number of INR-tester without AF as main diagnosis = (Total numbers of INR-tests pr warfarin user - number of INR-tests pr warfarin user). Here, we assume that these visits would take place in any case, regardless of whether patients use warfarin or NOACs.
- Estimated reduction in visits for AF patients = (Number of INR-tests pr warfarin user – 1) , Assuming that any patient would have at least one visit to his GP per year related to the AF diagnosis.
-

Table 13. Total estimated reduction in GPs/ private specialists INR-visits for the years (2009-2011)

Year	INR – Users Norway 2009-2013	INR-tests at GPs or private specialists	INR – tests Per warfarin-user	INR-tests with atrial fibrillation as main diagnosis	INR-tests with atrial fibrillation as main diagnosis-per user	INR –tests Per warfarin-user without atrial fibrillation	Visits with NOAC	Reduction in visits
2009	86318	928 955	10,76	378109	4,38	6,38	(At least) 6,4	3,38
2010	88630	979 059	11,04	399866	4,51	6,53	(At least) 6,5	3,51
2011	92131	1 049002	11,38	444171	4,82	6,56	(At least) 6,6	3,82
2012	94709							
2013	87994							
2013 Kunnskaps-senteret-estimate,			13				5	8
Boehringer Ingelheim assumptions in their application-Dabigatran,								16

7.4.1 Section 3 study: Impacts of reduced number of INR-test visits on the cost- effectiveness of NOACs compared to warfarin

Table 14. undiscounted and discounted reduced costs per patient per year

Year numbers	Undiscounted	Discounted
1	932,34	932,34
2	932,34	896,4808
3	932,34	862,0007
4	932,34	828,8469
5	932,34	796,9681
6	932,34	766,3155
7	932,34	736,8418
8	932,34	708,5018
9	932,34	681,2517
10	932,34	655,0497
11	932,34	629,8555
12	932,34	605,6303
13	932,34	582,3368
Total	12120,42	9682,42

Discounted values =Reduced cost per patient per year/(1+0.04))^(A9-1)

Where A9 is the year number.

Table 15. Impact on incremental net health benefit

Reduced cost per patient per year	932,34
Assumed remaining (quality adjusted) life years expectancy	13
Reduced cost per lifetime	12120,42
Reduced cost per lifetime (discounted)	9682,42
Willingness to pay threshold (NKR)	588 000
Impact on net benefit	0,016467

Impact on net benefit = Reduced cost per lifetime (discounted)/ 588000

= 0,016467

Assumed remaining (quality adjusted) life expectancy for a 65 year patient suffering from atrial fibrillation, with a medium risk of developing stroke was estimated to be 13 QALYs when treated with warfarin (discounted: 9.12 QALYs)

This estimate will not be exact, but illustrates approximately the impact of the number of INR-tests on the cost-effectiveness of NOACs compared to warfarin.

Table 16. Lifetime effects of oral anticoagulants when CHA2DS2-VASc=2

Oral anticoagulant	NHB	INHB	INHB after including reduced costs of Kr 932,- per year
Dabigatran 150	7.46	0.15	0.134
Apixaban	7.42	0.11	0.094
Dabigatran 150 ESC	7.41	0.09	0.074
Rivaroxaban	7.40	0.08	0.064
Warfarin	7.32		
Dabigatran 110	7.28	- 0.04	- 0.056

Source: HTA Report nr 5-2013

Dabigatran 110 above age 80 in NoMA and above 75 in ESC0,016

NTB (Net health benefit given WTP of NOK 588 000 per QALY)

INTB (Incremental net health benefit is the difference between NHB for each NOAC intervention and warfarin)

7.5 Section 3 study: Cost calculations

Costs associated with calculating the number of reduced INR-tests at GPs and private specialists' clinics in 2013 due to the introduction of NOACs for the treatment of atrial fibrillation, given the assumption that atrial fibrillation is the patients' main disease category, and that patients using NOACs need *only one control visit* to their doctor per year.

- Cost per GPs visit (NOK)= 229 for 2009, 237 for 2010 and 244 for 2011
  Source: http://www.legemiddelsiden.no/default.aspx?PageID=139
- Reduced costs per patient= (Reduction)* (Cost per GPs visit)
- Total cost reductions= Reduced costs per patient (NOK) * number of users
- Estimated reduced total costs by the Kunnskapsseneret = (number of users)*(estimated numbers of GPs visits)*(costs per visit)

- **Total costs for Dabigatran in 2013 (NOK) =9175*13 879 = 127 339 825**
- **Total costs for Rivaroxaban in 2013 (NOK) =7966*13 423 = 106 927 618**

- **Total costs for Apixaban in 2013 (NOK) = 2260 *9345 = 21 119 700**

- **Total costs NOACs in 2013 (NOK) = 255 387 143**
- **Total costs for warfarin in 2013 (NOK) = 87 994* 901 = 79 282 594**
- **Total costs (NOACS and Warfarin) = 334 669 737**

- **Costs for Dabigatran (NOK)**

  = (94 709)*(16)*(244) = 359 679 424

Table 17. Reduced Costs due to introduction of NOACs, and reimbursement costs for Dabigatran, Norway 2013

Year	Cost per visit	Reduced costs per patient	Reduced total costs	Reduced costs as estimated in the HTA Kunnskapssenteret Report 5-2013
2009	229	774,11	66 820 139	158 134 576
2010	237	832,27	73 762 932	168 042 480
2011	244	932,34	85 89 7760	179 839 712
At reimbursement application for Dabigatran				359 679 424

The formula used "in the Excel table" to calculate estimated reduced costs in the reimbursement application for Dabigatran:

Number of users in 2013 *Reduction in the number of patients' visits estimated by Boehringer-Ingelheim at their reimbursement application for Dabigatran * Cost of GPs, private specialists visit in 2013: NOK 244

= 92131*16*244 = 359 679 424 NOK

8 Key Findings

In this section, I will presents key- results obtained for each of the different thesis sections that were outlined earlier

8.1 Section 1 results

Where the purpose of the study was to estimate the numbers of INR-tests performed in Norway in 2009 and their societal costs, the following results were obtained:

Table 18. Estimated numbers of INR-tests and their estimated social costs for the year 2009

Estimated total numbers of INR-tests performed in Norway in 2009	1 783 202 tests
Estimated societal costs associated with INR-testing in Norway in 2009	NKR. 704 921 667

8.2 Section 2 results

Where the purpose was to estimate the number of INR-tests performed at GPs or private specialist between 2009-2011, the following results were obtained:

Table 19. Estimated numbers of INR-tests for the years(2009- 2011)

Year	INR – Users Norway 2009-2011	INR-tests at GPs or private specialists	INR – tests Per warfarin-user	INR-tests with atrial fibrillation as main diagnosis	INR-tests with atrial fibrillation as main diagnosis- per user	INR –tests Per warfarin-user without atrial fibrillation
2009	86318	928 955	10,76	378109	4,38	6,38
2010	88630	979 059	11,04	399866	4,51	6,53
2011	92131	1 049002	11,38	444171	4,82	6,56

8.3 Section 3 results

Where the purpose was to calculate number of INR- reduced GPs/ private specialists due to the introduction of NOACs and then to examine if such reduced visits for atrial fibrillation patients have any impact on the cost- effectiveness of NOACs compared to Warfarin by evaluating their incremental net health benefit. Furthermore, I proceeded to calculate the 2013 total usage- costs for Dabigatran, Apixaban and Rivaroxaban, compared to using Warfarin.

Table 20. Estimated total reductions in INR- visits to GPs/ private specialists for the years (2009-2011) due to the introduction of NOACs

Year	Gender	Estimated reduction in visits.	Estimated total visits' reductions
2009	Female	3,5	
	Male	3,3	3,38
2010	Female	3,7	
	Male	3,4	3,51
2011	Female	4,0	
	Male	3,7	3,82

Table 21. The numbers of users of warfarin and NOACs for the years (2009- 2014)

Year	Warfarin	NOACs
2009	86 318	54
2010	88 630	378
2011	92 131	2 037
2012	94 709	5 434
2013	87 994	29 562
2014	77 750	45 189

Table 22. Percentages of females using Warfarin for the years (2009- 2014), and females using NOACs for the years 2013 and 2014

	Males	Females	Percentage Females using Warfarin	Percentage females using NOACs	Percentage of females amongst all users of OAC
2009	51 713	34 605	40,1 %		40,1 %
2010	53 143	35 487	40,0 %		40,0 %
2011	55 322	36 809	40,0 %		40,0 %
2012	56 720	37 989	40,1 %		40,1 %
2013	52 803	35 191	40,0 %	43,6 %	40,9 %
2014	46 709	31 041	39,9 %	43,2 %	41,1 %

Table 23. Predicted number of users per 1000 for warfarin and NOACs from linear regression for the period (2004- 2014)

	Predicted number of users pr 1000 from linear regression	Number of Warfarin Users per 1000	Number of NOAC users pr 1000	Number of Oral Anticoagulants (Warfarin+ NOACs) users per 1000
0	19,3417	19,15	,	19,15
1	19,7975	19,85	,	19,85
2	20,2533	20,38	,	20,38
3	20,7091	20,88	,	20,88
4	21,165	21,17	,	21,17
5	21,6208	21,45	,	21,45
6	22,0766	21,75	,10	21,85
7	22,5324	22,31	,40	22,71
8	22,9883	22,53	1,21	23,74
9	23,4441	20,69	6,51	27,20
10	23,8999	18,08	9,90	27,98

Linear regression graph of warfarin users (2004- 2009) and predicted users for warfarin and NOACs (2004- 2014)

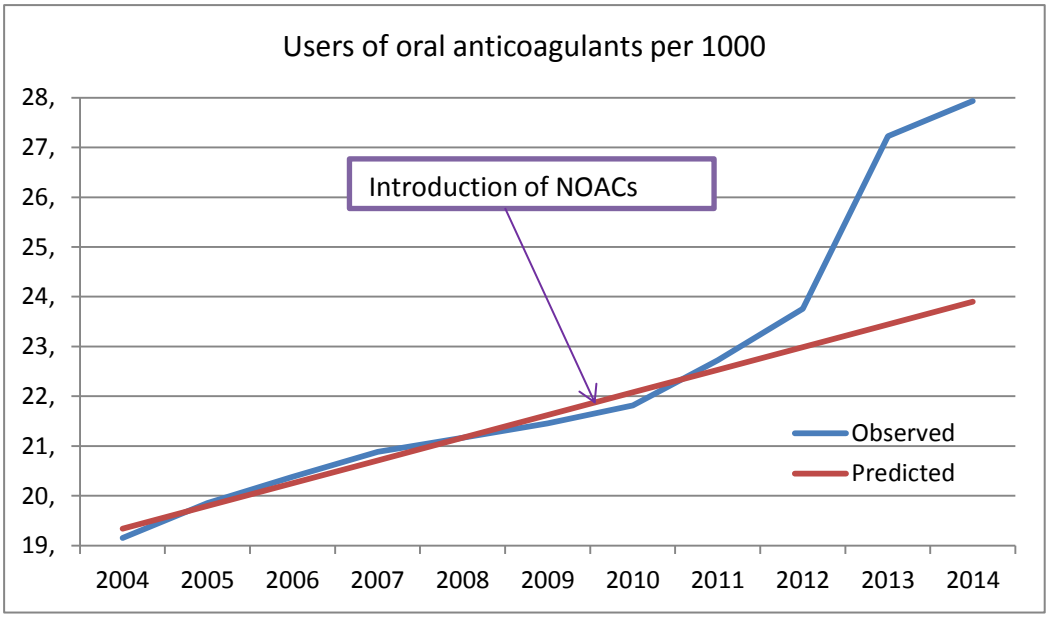


Figure 13. .linear regression graph of observed and predicted users of oral anticoagulants per 1000 between (2004- 2014)

Table 24. Linear regression output for users of oral anticoagulants per 1000

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	19,34166	0,122686	157,6516	9,71E-09	19,00103	19,68229
X Variable 1	0,455827	0,040522	11,24891	0,000356	0,34332	0,568334

When examining the impact of reduced number of INR-visits on the cost-effectiveness of NOACs compared to warfarin undiscounted and discounted reduced costs per patient per year, assumed remaining (quality adjusted) life expectancy for a 65 year patient suffering from atrial fibrillation, with a medium risk of developing stroke was estimated to be 13 QALYs when treated with warfarin (discounted: 9.12 QALYs) and 4 % discount rate.

Table 25. Total undiscounted and discounted reduced costs per patient per year

Assumed remaining QALYs expectancy	Undiscounted	Discounted
Total	12120,42	9682,42

Table 26. Impact of reduced costs per patient per year on the incremental net health benefit

Reduced cost per patient per year (NKR)	932,34
Assumed remaining (quality adjusted) life years expectancy	13
Reduced cost per lifetime (NKR)	12120,42
Reduced cost per lifetime (discounted NKR)	9682,42
Impact on net benefit	0,016467

Table 27. Incremental net health benefit for NOACS compared to Warfarin after including

The reduced cost of NKR 932 per year, based on HELFO data, 2011

Oral anticoagulant	NHB values in the HTA-13 report	INHB values in the HTA-13 report	INHB after including reduced costs of NKR 932,- per year
Dabigatran 150	7.46	0.15	0.134
Apixaban	7.42	0.11	0.094
Dabigatran 150 ESC	7.41	0.09	0.074
Rivaroxaban	7.40	0.08	0.064
Warfarin	7.32		
Dabigatran 110	7.28	- 0.04	- 0.056

Table 28. Reduced Costs due to introduction of NOACs based on reduced numbers of GPs visits, and reimbursement costs for Dabigatran, Norway 2013

Year	Cost per visit	Reduction in visits	Reduced costs per patient	Reduced total costs	Reduced costs as estimated in the HTA Kunnskapssenteret Report 5-2013
2009	229	3,38	774,11	66 820 139	158 134 576
2010	237	3,51	832,27	73 762 932	168 042 480
2011	244	3,82	932,34	85 89 7760	179 839 712
Reimbursement application- Dabigatran					359 679 424

Table 29. Total costs of NOACs and Warfarin use in 2013 (NOK)

oral Anticoagulants	2013	Price per year (NOK)	Total Cost in 2013 (NOK)
Warfarin	87994	901	79 282 594
Dabigatran Etexilate	13879	9175	127 339 825
Rivaroxaban	13423	7966	106 927 618
Apixaban	2260	9345	21 119 700
All 3 NOACs			255 387 143

Source: Norwegian Prescription Database

http://www.reseptregisteret.no

Report date: 29/05/2014 18:09

9 Analysis and Discussion

Data collection for estimating the total numbers of INR test in Norway in 2009 was straightforward. Similar to other surveys, some respondents needed both email and telephone reminders before sending us their data. Response rate to our survey was 90 %, indicating excellent status when compared to average response rates of surveys in general (Appendix 2a). Dillman (2000) reported that 70% response rate could be produced consistently with careful attention to design and question formats. Kittleson (1997) outlined the importance of follow up notices when performing electronic based surveys. Furthermore, he reports that an email survey would commonly produce 25% -30% response rates without any follow up (Kittleson, 1997 p. 196). Incentives and academic settings were described by Sheehan and McMillan (1999) as being relevant important factors for raising response rates in email based surveys. This relates well to our own survey, which was email based and both academic and scientific in nature where many scientists, doctors, health economists, policy makers, hospital administrators, health departments, and the pharmaceutical industry, amongst many others, have vested interests in proper estimates to quantify costs associated with INR testing since it places a great burden on annual health budgets. Holbrook et al., (2005) examined the relationship between surveys 'response rate and demographic representativeness of the sample chosen they reported that "lower response rates decreased demographic representativeness within the range examined". This fits well with our own presumption of good representation between numbers of tests done at Østfold and Norway as a whole. Under ideal study situations, such a survey would have been done for all Hospitals in Norway. This would have given us a platform to do statistical significance analysis of empirical data collected and to, for example, examine standardized regression coefficients.

To our knowledge, there were no other similar studies, at the time, to place the numbers of INR-tests performed per year in the proper economic context with respect to health expenditures, reimbursement costs and budgeting for subsidizing patients' use of potentially good new oral anticoagulants in Norway.

The formulation of our email request was friendly, short and explicit. We explained the purpose of our study and the specific data required. We addressed the email to lab chiefs, thus avoiding time-consuming interferences and possible delays when non-related personnel get involved (Appendix 11). In addition, Professor Ivar Sønbø Kristiansen has many healthy

professional and sustainable contacts with many people in the health sector, so our request was taken seriously, facilitating good response rate.

Based on our collected data from SØ-HF, the 2009 total number of INR-test were 835,202 tests. Complete data from Østfold county hospitals indicated *46, 741* in a population of *268,548* (SSB, 1 January 2009). This represents an average *1740* tests per *10,000* population.

Our collected data (Total INR-test, in Norway in 2009= *835,202*) was slightly biased down since 2 hospitals didn't reply to our survey. We therefore, saw it appropriate to adjust our estimates based on the collected data from Østfold region. This gave us a new estimated total INR-test number for the whole of Norway in 2009 equaling to *949,091*.

The Norwegian Health Economics Administration (HELFO) reports indicate 902,200 INR tests were reimbursed by HELFO during the period 1st of July 2008 through 30th of June 2009. For the previous period, number of performed INR tests was 844 000 (source Steinar Mathisen, Directorate of Health, Oslo). We therefore, used 902,200 as an estimate of the total number of tests performed during 2009.(Kristiansen I.S, report of 30.07.2010), With permission.

To calculate societal costs associated with INR testing in Norway in 2009, an estimate of total number of tests is required, including tests from GPs and other private specialists, commercial laboratories and some other labs performing INR-testing.

The number of INR-tests according to type of patients and type of lab in Norway, in 2009 was estimated to be *1 783 202 tests* (Table 4, page 32)

Societal cost types were specified and based mainly on fee-schedules, not market prices, so actual costs may vary. Where doctors take blood samples for sending, costs were increased dramatically as proportions of total costs. In direct costs were difficult to estimate, so a "common-sense" approach is used for such estimations.

This estimate however doesn't take into consideration intangible costs associated payments form the welfare system to patients due to psychosomatic illness a result of worry and anxiety, and how that may affect the frequency of their contact with health personnel, resulting in additional costs.

Total societal costs for INR-testing in Norway for 2009 were estimated at NOK 704 921 667, Which are considerable and would probably constitute a major burden on Norwegian health-care expenses and budgeting. Our estimate would hopefully be recognized as an input to help policy makers to identify the economic implications associated with the magnitude of INR-testing in Norway, and justify the allocation of funds to aid research, intervention programs, prevention and control initiatives, and to health- program evaluations within an economic framework. Such INR- social costs estimates may also support continued "public policy debates" (Segel 2006). This resonates well with the description of the burden of disease by the WHO, as "input to health decision making and planning" (WHO, 2010).

Direct and indirect costs associated with an illness or an intervention is worked using a bottom up approach, by looking at different activities and available resources used, and multiplying up by unit costs. The amount of the activity is therefore an indicator of the likely financial cost, even if the costing hasn't been completed. Activities may vary, and some activities may be missed when performing an economic evaluation of costs, therefore, total societal costs associated with INR-testing in Norway may still be higher than the estimated costs of NOK 704 921 667 for 2009.

One may however argue that maintaining INR values within the recommended range could lead to some cost offsets in health care costs by avoiding strokes, and reduced demands for the relatively more costly stroke care.

A future prospective study would probably be interesting to evaluate changes of such costs due to the therapeutic introduction of new oral anticoagulants in the Norwegian health system.

INR-testing and the use of Warfarin are very strongly associated to incidence and prevalence of atrial fibrillation. Our HELFO data collected for the years (2009-2011) show that about 75% of all INR tests were performed for patients where AF was the main diagnosis.

Amongst the Norwegian population, AF is registered as the most common cardiac arrhythmia, with a prevalence of 1.5–2% in the general population (Go AS, Hylek EM, Phillips KA, et al, 2001 ; Camm et al., 2012). And its prevalence increases with increasing age, to about 10% among 75-year-olds and to about 18 % in people aged over 85 years. The prevalence is highest among men, around 15% by 75 years of age (Tveit et al., 2008). This is probably due to the incidences of other old-age related diseases, including diabetes and hypertension (Kirchhof et al., 2012). Feinberg WM, et al., (1995) reported that AF is comparable for men

and women, with a steep increase in women over 80, producing a higher risk of stroke. The authors attribute this to" mortality displacement", producing stronger correlation between atrial fibrillation and fatal strokes for men before they are 80 years old older. Camm et al., (2010) report that atrial fibrillation «It is somewhat higher in men than in women, and has increased over the past few decades".

Estimates of incidence and prevalence vary between different countries, and across Europe, it is estimated that about six million people suffer from AF (Camm et al., 2010). In a European hear survey, 39 % of respondents reported that AF was an underlying health condition (Nieminen et al, 2006). In Denmark AF prevalence is about 4.38 per 1000 inhabitants aged 40-89 years (Frost et al, 2005) , in Italy about 7.4 % of those aged 65+ (Bilato et al., 2009),in the Netherlands, about 5.5 % of those aged 55+ (Heeringa et al., 2006), in Portugal, about 2.5 % those aged 40+ (Bonhorst et al., 2010), in Spain , about 8.5 % of those aged 60+ and in the UK, about 1 % prevalence (BJHM, 2009). The prevalence of AF is expected to increase over time and is may be doubled in the next 50 years (Camm et al., 2010 ; Rietbrock et al., 2008).

A major challenge for doctors is the early diagnosis of AF since it is silent disease having no clear symptoms and may therefore go undiagnosed for many patients, for a long time (Camm et al 2010). This means that , in practice, prevalence of AF, and subsequently its management real costs are most likely to be underestimated.

Our collected HELFO and prescription registry data correlates INR-testing to prevelance of AF as a main diagnosis and to warfarin use. The data shows a gradual and steady increase of performed INR- tests for the years (2009-2011) for both men and women where AF was the main diagnosis (tables 6, 7 and 8, pages 35 and 36) . This corresponds to literature estimates of increased prevalence of atrial fibrillation over time.

About 222 000 tests for men and 157 000 tests for women in 2009, compared to 260 000 for men and 184 000 test for women in 2011, respectively. A similar trend is shown by the total number of INR-tests performed for the same period. Irrespective of main diagnosis, about 540 000 for men and 389 000 for women in 2009 compared with 612 000 for men and 436 000 for women in 2011, respectively. This represents a progressive total increase of *4.1%* between 2009 -2010, and *3.6%* increase for 2010-2011. This is surprising, since one would have expected a slight decrease in these numbers of between 2010-2011 due to the introduction of new oral anticoagulants as alternatives to warfarin in some thromboembolic therapy practices

in 2010. This is probably due to NOACs therapies were insignificantly small at that period, that no change is marked. It is difficult for me to analyze this at face-value, but most probable contributing reasons might relate to increasing market segments of NOACs in Norway, better marketing strategies from manufacturers, little acceptance of doctors to start with alternative therapies to warfarin, or it might also reflect the reluctance of some doctors to change their therapy practices vis-à-vis their patients if patients conditions are stable, and if patients were happy with their health/ medication status-quo. In the year 2014, Dabigatran had *15 357* users; Rivaroxaban had *20 792* users and Apixaban had *8640* users, so the data relating to this is so fresh and small that we might need to set up a new experimental design to study change rates in administrating the therapeutic use of NOACs in Norway in the future.

Feinberg WM, et al., (1995) reported that AF is comparable for men and women, with a steep increase in women over 80. On the other hand, Tveit et al. (2008) reported that its prevalence is highest among men, around 15% by 75 years of age, and Camm et al., (2010) reported that atrial fibrillation" is somewhat higher in men than in women, and has increased over the past few decades". Comparing this to our data collected from the prescriptions registry data for warfarin and NOACs, (table 10, page 37), about *40.1 %* of warfarin users in 2009 were women, compared to *39.9 %* female-users in 2014. For NOACs, *43.6 %* of users in 2013 were females, compared to *43.2 %* in 2014. It is difficult for me to explain gender differences with respect to percentage use of warfarin and NOACs, but a possible explanation is that women were probably underdiagnosed group with respect to AF and other thromboembolic diseases , and that warfarin users are mainly patients that were diagnosed earlier, while NOACs users are patients that are diagnosed more recently. Advances in diagnostic technology and better detection and treatment guidelines would also have facilitated earlier and wider detection of thromboembolic conditions amongst women as well as men. Our oral anticoagulants' data was not stratified according to different age groups as this was out of the scope of this study.

Approximately at the same time as the introduction of NOACs, there was also a change in risk scoring system, from CHADS2 to CHA2DS2-VASc where different risk factors indicate increased risk of stroke among patients with atrial fibrillation. Total score ranges from 0 to 9.

scoring per risk factor include : Age>75 = 2, Vascular disease = 1, Diabetes mellitus = 1, Hypertension = 1, Prior Stroke/TIA/thromboembolism = 2 and sex (female) = 1.

CHA2DS2-VASc risk score acknowledges that women with atrial fibrillation have higher risk of stroke, and hence better awareness and understanding of AF amongst doctors would probably translate into more women being diagnosed and treated, with better outcomes for patients and less demand on the health- care system.

To predict the number of users of oral anticoagulants per 1000, prescription data for warfarin (2004-2009) was used and a simple linear regression was made (Table 23, page 45).

A graphical stacked area plot for users of oral anticoagulants per 1000 inhabitants for warfarin and NOACs for the period (2004- 2014) is shown below,

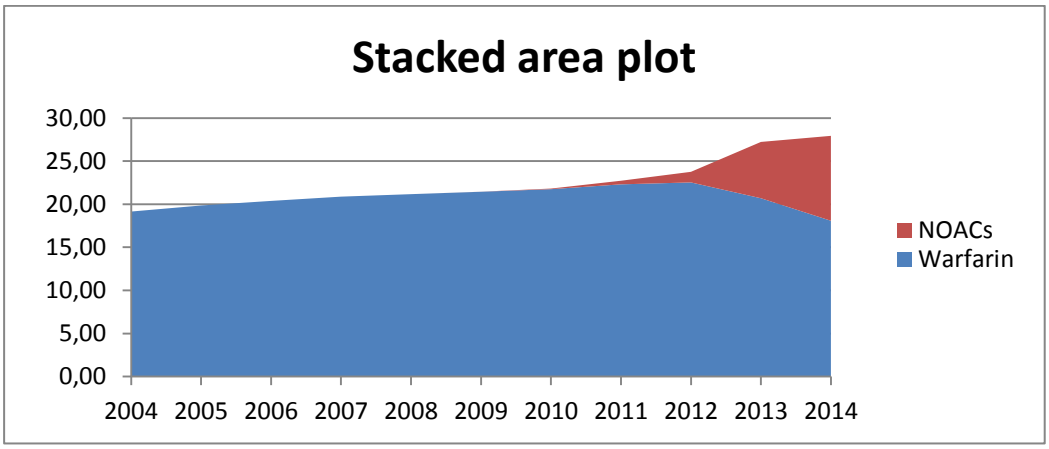


Figure 14. .Stacked area plot for Warfarin and NOACs for the years (2004- 2014)

The graph shows an overall increase in the use of oral anticoagulants regardless of gender. There is a reduction of warfarin use from around 2012, probably due to newly diagnosed AF patients being treated with NOACs, whilst the majority of older warfarin users continued using warfarin. Some of those patients might also have died, thus diminishing total warfarin use accordingly. Limitations of this data are that it doesn't reflect the percentage of warfarin users that were transferred to using NOACs. instead by their doctors.

Output of linear regression graph (figure 13, page 46) of observed (2004- 2009) and predicted users of oral anticoagulants per 1000 (2004- 2014) is shown below:

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	19,34166	0,122686	157,6516	9,71E-09	19,00103	19,68229
X Variable 1	0,455827	0,040522	11,24891	0,000356	0,34332	0,568334

Where the X-variable is the users per 1000

This means that the increase in users' anticoagulants per year 95% coefficient is about 0.5 per 1000 inhabitants (0.458). So, if we assume a ca 0.5 coefficient increase after the year 2009, then the red- regression line representing predicted number of users of oral anticoagulants per 1000 inhabitants,(in figure 13) shows the expected increase in anticoagulants use over time. This coefficient lies in-between the lowest 95% coefficient interval (0.34) and the highest 95% coefficient interval (0.56).

For the year 2004, It was estimated 19.3 users per 1000 inhabitants of warfarin. If we add about 0.5 user per 1000 for each subsequent years, or in other words, 1 user per 2000, the red line would represent an estimated continued increase per year based on entry data between (2004-2009). The P- value is much lower than 0.05, indicating strong significance.

The limitation of this data is that we used only 6 points in the linear regression. Ideally a minimum of 10 points better be used to give better prediction. Nevertheless, the graph shows an increase in oral anticoagulant use between (2004-2014), and an estimated *17 %* more patients using oral anticoagulants than predicted.

Addressing the relationship between cost- effectiveness of NOACs compared to warfarin, as described in the HTA- 2013 report, and reduced GPs/ specialists' number of visits by AF patients due to the introduction of NOACs, based on HELFO-data for the years (2009-2011), we estimated total number of INR-tests and number of INR-tests among those with atrial fibrillation as a primary diagnosis for males and females. Number of warfarin users were taken from the Norwegian prescription registry. By dividing number of INR tests by number of warfarin users, we get estimates of number of INR tests per warfarin users. If we assume that only those visits with atrial fibrillation as a primary diagnosis could be eliminated due to introduction of NOACs, and that patients with atrial fibrillation would have at least one GP visit with atrial fibrillation as primary diagnosis, the estimated reduction in visits due to the introduction of NOACs would be between 3,3 and 4,0 visits (table 12, page 38).

Using the same QALYs assumptions made in the HTA-report with respect to assumed remaining (quality adjusted) life expectancy for a 65 year patient suffering from atrial fibrillation, with a medium risk of developing stroke was estimated to be 13 QALYs when treated with warfarin (discounted: 9.12 QALYs), and where reduced cost per patient per year is about NKR 932, then the reduced cost per lifetime would be NKR 12 120 (discounted: NKR 9682). This gives an added impact on the incremental net health benefit of *0, 0165*

(table 26, page 47), where the impact on the incremental net health benefit = Reduced cost per lifetime (discounted)/ 588 000. This calculation is based on the willingness to pay threshold for cost-effectiveness of NOK 588 000 per QALY in the year 2011.

In their HTA- 2013 report , the authors examined the relationship between mean incremental costs vs incremental effectiveness of NOACS with respect to warfarin. Their results are displayed as strategies along a willingness to pay cost-effectiveness frontier line. They ranked their strategies according to incremental net health benefit (INHB) , where the point furthest away from the WTP line is the most cost effective intervention (Appendix 17).

Incremental net health benefit is the difference between net health benefit (NHB) for each NOAC intervention and warfarin.

They conclude that all three oral anticoagulants, Dabigatran 150mg, Rivaroxaban 20 mg and Apixaban 5mg were cost- effective when each of them was compared to warfarin for patients with medium – high risk of developing stroke. When they were compared to each other, Dabigatran 150mg was the most cost-effective, with an INHB of *0.15*, followed by Apixaban, with an INHB of *0.11*, then Dabigatran ESC, with an INHB of *0.09*. Raviraxaban was least cost effective, with an INHB of *0.08.*

Dabigatran 110 mg for the same risk group had a negative INHB of *-0.04*, indicating that it was not cost effective compared to Warfarin.

After including the reduced cost- effect of NKR 932 per year, which is based on our HELFO data for 2011, The INHB for NOACs compared to Warfarin were *0.134* for Dabigatran 150, *0.094* for Apixaban, *0.074* for Dabigatran 150 ESC, *0.064* for Rivaroxaban and – *0.056* for Dabigatran 110 (table 27, page 47).

Even though our INHB values are rough estimates, and assuming a WTP cost effectiveness threshold of NKR 588 000, and 13 expected remaining QALYs then we save about NKR 9682 (table 15, page 40), which, in theory, produces some sort of health benefit of 0.0164 value for a 65 year old AF patient with moderate risk of developing stroke if treated with warfarin.

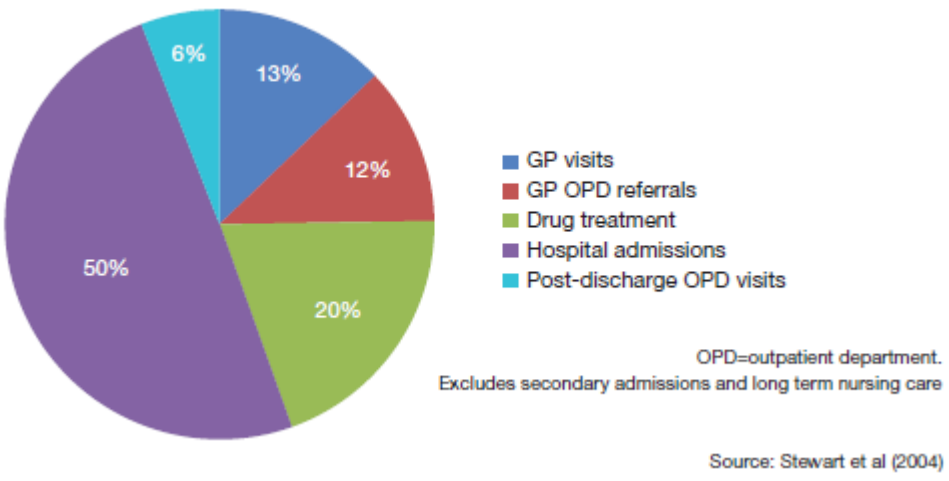
This means that the incremental net health benefit effects of reduced INR- visits to GPs/ private specialists to such type of patients is far too small to have any effect on the cost effectiveness of using any of the NOACS, Dabigatran, Apixaban or Rivaroxaban as compared

to using Warfarin. This small benefit might however be marked somewhere else in the health system, for example, as reduced waiting time at the doctors office.

Addressing total reduced visit-costs due to the introduction of oral anticoagulants in Norway in 2013, and reimbursement costs for Dabigatran in 2013, when Boehringer Ingelheim submitted a reimbursement report to the Norwegian Medicines Agency (NoMA) for its Dabigatran drug.

An argument pharmaceutical companies use when applying for drug and reimbursements approvals so that expensive drugs used for chronic diseases, such as thromboembolic disease may be covered using the " blå resept" arrangement, is often strongly based on economic evaluations, provided that health benefits are established. In the case of NOACs, shifting therapy types from Warfarin based, would arguably lead to reductions in the number of AF patients' visits to their GPs or private specialists, and reduced costs since no INR- monitoring is required any longer. This monitoring process is costly, and must therefore be accounted for in any cost-benefit analysis.

There is no clear consensus on the levels of such visit reductions in the literature, nor any figures from Norwegian data registries were found, as to the representations of AF related GP visits with respect to direct health care costs. Stewart et al., (2004) reports GP visits for British AF patients representing 12 % of UK direct health care cost, as seen below:



Source: Stewart et al., 2004: reported in the atrial fibrillation awareness and risk education report, 2010

The number of INR- visits per warfarin user per year vary, and range from about 9.2-16.2 ((HTA Report no 5-2013) In Norway, an approximate number of "13" INR- visits is used (Statens legemiddelverk Refusjons rapport, 2012), compared to " 16.2" in Swedish reports (Bjorholt I et al., 2007). This was the same number of visits that Boehringer Ingelheim used for their Dabigatran reimbursement application to the Norwegian Medicines Agency.

For patients using NOACs, NoMA assumes they still use 5 GP/ private specialist visits per year. And the authors of the HTA -13 argue for the same patients using about 5 visits.

Such reported figures in the above mentioned literature contradict our findings in this study where our data for patients having INR-test based on AF as their main diagnosis disease, show reductions of visits of *(3.8, 3.51 and 3.82)* for the years 2009, 2010 and 2011 respectively (table 13, page 39).

Reduction in INR-visits per patient per year =

(INR tests per warfarin user with atrial fibrillation as main diagnosis – 1) , assuming that such patients would need a minimum of 1 visit per year to their GP for a check up.

The estimated number of visits reductions used in the HTA-13 Report was *8*, and Boehringer Ingelheim used *16* visit- reductions for reimbursements costs relating to Dabigatran.

Based on this, our findings show reduced total costs due to the introduction of NOACs are in the order of NKR 67 mill for 2009, NKR 74 mill for 2010 and NKR 86 mill for 2011 Comparative reduced costs as estimates in the HTA-13 report. were in the order of, NKR *158 mill* for 2009, NKR *168* mill for 2010 and NKR *179* mill for 2011 .

For Dabigatran, at reimbursement application, about NKR *340 mill* reduced costs were estimated.
Our assumptions were explicit in sense that visit reductions related only to one main diagnosis, and that only 1 GP/ private specialist's visit is made by patients using NOACs per year. Such assumptions are widely open to criticism and may influence the validity and reliability of our findings. Bias issues were not addressed since we had no vested interests or strong biases to using any specific methods for either data collection or data analysis, which was done fairly recently in collaboration with Professor Ivar Sønbø Kristiansen and Associate Professor Torbjørn Wisløff at the Department of Health Economics and Health Management at the University of Oslo.

10 Conclusion

Atrial fibrillation is a complex disease to diagnose and manage, depending on changing patients' characteristics. It uses substantial resources across primary and secondary health care. Appropriate management of therapies is a key driver to reducing direct and indirect costs, especially in regions and times where health care resources are limited. Having well established guidelines, and moving practice closer to guidelines would offer patients better health outcomes and reduce comulative costs associated with AF.

Societal costs associated with INR-testing in Norway for 2009 were estimated at about NKR 705 million, which are quite substantial and place a heavy economic burden on the Norwegian health system. Replacing Warfarin therapy with NOACs for atrial fibrillation patients would offset some of these costs, but resultant economic savings for such patients in terms of their reduced GPs/ private specialists visits are over-estimated in the HTA-13 report and by Boehringer Ingelheim. Actual reduced INR-visits for AF patients using NOACs are between (3-4) reduced visits. This would translate into INR-visits economic savings in the order of NKR (66-86) millions, which are roughly half of the reported savings of NKR (150-180) millions. In 2013, Norwegian patients used an estimated 255 million NOK on NOACs and 79 million NKR on Warfarin, which are considerable. Reduced visit-costs at reimbursement application time for Dabigatran were estimated at NOK 360 000 000, which were unrealisically high.

Had the Ministry of Health accounted for this level of reduced INR visit-costs when handling reimbursement applications for the different new oral anticoagulants (NOACs), then about NOK 100 million extra should have be budgeted for at the introduction of NOACs as alternative drugs to Warfarin for atrial fibrillation patients, assuming there is a total change to new therapies.

Cost effectiveness for NOACs would NOT change with respect to reduced numbers of GPs/ private practitioners visits for INR-patients, as they appear in the HTA-13 report since the incremental net health benefits obtained based on such reduced INR-visits are too small, but the effects may however, be intangible benefits to such patients, somewhere else in the health system.

11 Limitations

In addition to time limitations affecting all of us, other limitations here relate to our choice of data collection methodology, type of data used with respect to whether we should have used INR-test data for longer than 3 years period, since warfarin therapy is long established, and perhaps to support this by including other international data to examine any variations based on different cultural approaches to such therapy in different health systems. The quality of data registered might also be examined, with respect to its recording and maintenance in different health data registries.

In our analysis, we tried our best to handle this data meticulously, and checked numbers and calculations over and over again to give this study good reliability and internal validity, that would hopefully allow us to make some generalizations with respect to our findings.

We had extended our empirical data collected in the first and second sections of this study, from INR-test numbers in South-East Health Region to the larger population of all Norwegian hospitals and other health facilities offering INR testing. We undertook some general assumptions that might be questionable with respect to assuming representativeness of INR-test practices across the country.

Our indirect cost estimates are mostly approximates, but we deliberately biased them down when possible.

There is a lack of studies to follow patients switching from warfarin to NOACs, therefore percentage of reduced number of GPs/ private practitioners visits as a result of changing INR-management is unknown.

12 Scope for Further Work

Our findings could open for two potential studies :-

The first would set up an experimental design to identify possible different affordances and constraints within the Norwegian health system that affect moving patients on Warfarin to NOACs therapy for different thromboembolic chronic patients, and compare that to other practices in different European countries.

The second would be draw upon cost estimates for stroke and correlate that to AF costs, and explore the potential of extrapolating available data to countries where no such data exists.

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Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital; NICE Clinical Guideline (January 2010)

Appendices

Appendix 1.

Total number of deaths in Norway due to acute myocardial infarction, pulmonary embolism, cerebrovascular diseases and atherosclerosis for both sexes, between 45 and 84 years old. For the years 2000-2012

Deaths by diseases of the circulatory system, by sex, age, cause of death, time and contents														
			2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
			Deaths	Deaths	Deaths	Deaths	Deaths	Deaths	Deaths	Deaths	Deaths	Deaths	Deaths	Deaths	Deaths
Both sexes	45-54 years	Diseases of the circulatory system (I00-I99	400	400	372	308	303	312	308	292	285	279	285	277	266
		Acute myocardial infarction (I21-I22)	183	178	147	130	132	118	121	106	93	102	109	103	94
		Pulmonary embolism (I26)	3	9	9	4	7	4	3	6	10	6	4	6	4
		Cerebrovascular diseases (I60-I69)	82	66	62	64	51	55	52	59	62	44	54	56	46
		Atherosclerosis (I70)	1	2	3	1	1	1	4	5	1	0	0	2	2
	55-64 years	Diseases of the circulatory system (I00-I99	812	860	815	756	797	748	811	781	791	720	729	669	717
		Acute myocardial infarction (I21-I22)	339	356	354	276	284	291	304	304	261	259	263	210	234
		Pulmonary embolism (I26)	6	6	6	5	5	5	11	6	12	7	12	7	11
		Cerebrovascular diseases (I60-I69)	120	160	145	115	150	123	139	129	164	129	124	128	121
		Atherosclerosis (I70)	7	10	3	8	6	7	10	10	13	5	8	6	5
	65-74 years	Diseases of the circulatory system (I00-I99	2463	2221	2207	1992	1807	1619	1486	1548	1435	1436	1389	1399	1420
		Acute myocardial infarction (I21-I22)	930	797	821	724	607	507	488	457	492	446	412	420	404
		Pulmonary embolism (I26)	22	15	21	23	26	17	12	20	20	16	17	19	24
		Cerebrovascular diseases (I60-I69)	493	457	480	427	420	379	311	324	298	329	287	314	309
		Atherosclerosis (I70)	43	43	50	31	32	30	23	31	31	14	33	23	27
	75-84 years	Diseases of the circulatory system (I00-I99	7130	7061	6661	6042	5772	5030	4829	4628	4360	3943	3771	3524	3500
		Acute myocardial infarction (I21-I22)	2146	2136	1996	1834	1767	1440	1262	1240	1199	1030	1023	906	837
		Pulmonary embolism (I26)	44	58	61	66	60	39	46	46	52	37	33	35	39
		Cerebrovascular diseases (I60-I69)	1848	1756	1707	1504	1454	1362	1277	1170	1206	1073	992	984	927
		Atherosclerosis (I70)	142	165	125	109	109	78	99	100	84	67	57	61	62
	Total		17214	16756	16045	14419	13790	12165	11596	11262	10869	9942	9602	9149	9049

https://www.ssb.no/a/english/kortnavn/dodsarsak_en/tab-2011-10-14-01-en.html (22.03.2014)

Appendix 2. Hospital laboratories performing INR-tests in South-East Regional Health Enterprise, Norway 2009. Laboratories in read did not respond to the data request.

1. Ahus
2. Diakonhjemmet sykehus Laboratorium
3. Kongsberg sykehus Laboratorium
4. Lovisenberg Diakonale Sykehus as Klinisk kjemisk Laboratorium
5. Martina Hansens Hospital laboratorium
6. Oslo universitetssykehus Aker Sentrallaboratorium
7. Oslo universitetssykehus Radiumhospitalet Sentrallaboratorium
8. Oslo universitetssykehus Rikshospitalet Hematologisk laboratorium
9. Oslo universitetssykehus Ullevål Laboratoriemedisinsk klinikk
10. Oslo universitetssykehus Ullevål Medisinsk biokjemi og klinisk farmakologi
11. Sykehuset Asker og Bærum Sentrallaboratoriet
12. Sykehuset i Vestfold Sentrallaboratoriet
13. Sykehuset i Vestfold Sentrallaboratorium Larvik/ Sandefjord
14. Sykehuset Innlandet Klinisk kjemisk laboratorium Elverum
15. Sykehuset Innlandet Klinisk kjemisk laboratorium Hamar
16. Sykehuset Innlandet Klinisk kjemisk laboratorium Lillehammer
17. Sykehuset Innlandet Klinisk kjemisk laboratorium Tynset
18. Sykehuset Innlandet Laboratoriemedisin Gjøvik
19. Sykehuset Telemark Enhet for medisinsk biokjemi og blodbank
20. Sykehuset Telemark Kragerø Laboratorium
21. Sykehuset Telemark Laboratorium Notodden/ Rjukan
22. Sykehuset Østfold Sentrallaboratorium (Askim, Moss, Halden, Sarpsborg og Fredrikstad)
23. Sørlandet sykehus HF Laboratorium Arendal
24. Sørlandet sykehus HF Laboratorium Kristiansand
25. Sørlandet sykehus HF Laboratorium Flekkefjord
26. Vestre Viken HF: Sykehuset Buskerud

Appendix 3. Total INR-tests_Hospitals_SØ-HF, Norway in 2009

Hospital	Inpatients	Internal Outpatients	External Outpatients	Total	Comments
AHUS	22095	18314	7399	47808	All tests performed at Central Lab
OUS Rikshospitalet	40407	9911	1076	51394	254: from different projects
Sykehuset Innlandet: Gjøvik	4776		1987	6763	Inpatients INR-tests include emergency and accute.
Sykehuset Innlandet: Lillehammer	31923	7709	11471	51103	External outpatients INR-tests include some projects
Sykehuset Innlandet: Elverum	3030	1282	1742	6054	Some outpatient INR-tests include accute
Sykehuset Østfold HF				46741	Total numbers are for ALL labs under SØ: Askim, Moss, Halden, Sarpsborg og Fredrikstad
Martina Hansens Hospital	614	82		696	82 :INR-tests are for all outpatients
Vestre Viken HF: Sykehuset Buskerud	12903	5742		18645	
Sykehuset i Vestfold HF: Sentrallaboratoriet	14925	8914		23839	8914 :INR-tests are for all oupatients
Sentrallaboratoriet Larvik/Sandefjord	92	53	80	225	External outpatients INR-tests include general practitioners and institutions
Avdeling for medisinsk biokjemi, Ullevål	33484	6277	2204	41965	632 :INR-tests are unspecified and for research
Hematologisk forskningslaboratorium, Ullevål		1414		1414	Only from outpatients
Sørlandet Sykehus, Arendal	6883		4818	11701	4818: INR-tests for all outpatients
Sørlandet sykehus HF, Kristiansand	13081		5903	18984	5903: INR prøver for all oupatients
Sykehuset Telemark HF, Skien	9256	3715	4909	17880	
Sykehuset Telemark HF: Notodden	2914	496	1285	4695	In addition, quality control tests and re-analysis of abnormal values
Vestre Viken HF, Kongsberg sykehus	3832	922	2056	6810	
Vestre Viken HF, Ringerike sykehus				9252	
Vestre Viken HF, Asker og Bærum sykehus	14000	2816	6470	23 286	2816 INR: taken at the thrombosis otpatient clinic
Lovisenberg Diakonale sykehus	8583	1900	3101	12584	
Sørlandet sykehus HF Flekkefjord	2285	386	393	3064	
TOTAL	**225083**	**69933**	**54894**	**404903**	

Appendix 4. Total adjusted INR-test numbers for 2009 from different hospitals, according to type of patients, in South-East Regional Health Enterprise, Norway

Hospital Nr. INR-Tests	Inpatients	Internal Outpatients	External Outpatients	Total numbers
TOTAL	250795	76856	62623	447517

The Norwegian Health Economics Administration (HELFO) reports indicate 902,200 INR tests were reimbursed by HELFO during the period 1st of July 2008 through 30th of June 2009. For the previous period, number of performed INR tests were 844 000 (source Steinar Mathisen, Directorate of Health, Oslo). We therefore, used 902,200 as an estimate of the total number of tests performed during 2009.

(Kristiansen I.S, report of 30.07.2010). With permission

Commercial laboratories

Two commercial clinical chemistry laboratories (Fürst Medisinsk Laboratorium and Unilab/Capo) offered testing to doctors and institutions (source: Fürst Medisinsk Laboratorium). In the spring of 2010 Fürst and Unilab merged, and data on INR tests were therefore obtained from Fürst. Here, it was reported that the two laboratories performed in total 35,800 tests in 2009. This number is well in line with data from HELFO. (Kristiansen I.S, report of 30.07.2010). With Permission.

Other laboratories

Presumably, some large nursing homes, private health care providers (Volvat Medisinske Senter , Feiringklinikken, *etc.*) and various other health care institutions (rehabilitation units, *etc*.) have laboratory equipment for taking INR-tests. We have no information about the test volumes here, but presumably they are limited. For completeness, we assume that in total 10,000 tests are taken, and that 50% were for in-patients and the rest for out-patients .These estimates imply that in 2009, in total approximately 1.8 million INR tests were taken . Among those, approximately 0.5 million were taken on in-patients.

Source: (Kristiansen I.S, report of 30.07.2010). With permission.

Appendix 5. Coding categories for different diagnosis

ICPC-2 Coding categories for different diseases used in Norwegian health services

Kapittel	Tekst	Symptomer og plager	Prosesskoder	Sykdoms-diagnoser:
A	Allmenn og uspesifisert (General and unspecified)	1-29	30-69	70-99
B	Blod, bloddannende organer og immunsystemet (Blood, blood forming organs, lymphatics, spleen)	1-29	30-69	70-99
D	Fordøyelsessystemet (Digestive)	1-29	30-69	70-99
F	Øye (Eye)	1-29	30-69	70-99
H	Øre (Ear)	1-29	30-69	70-99
K	Hjerte-karsystemet (Circulatory)	1-29	30-69	70-99
N	Nervesystemet (Neurological)	1-29	30-69	70-99
P	Psykisk (Psychological)	1-29	30-69	70-99
R	Luftveier (Respiratory)	1-29	30-69	70-99
S	Hud (Skin)	1-29	30-69	70-99
T	Endokrine, metabolske, ernæringsforhold (Endocrine, metabolic and nutritional)	1-29	30-69	70-99
U	Urinveier (Urology)	1-29	30-69	70-99
W	Svangerskap, fødsel, familieplanlegging (Pregnancy, childbirth, family planning)	1-29	30-69	70-99
X	Kvinnelige kjønnsorganer (inkl. bryst) (Female genital system and breast)	1-29	30-69	70-99
Y	Mannlige kjønnsorganer (Male genital system)	1-29	30-69	70-99
Z	Psykososiale og sosiale problemer (Social problems)	1-29		
L	Muskel-skjelettsystemet (Muscular and skeletal)	1-29	30-6	70-99

Source: Kompetansesenter for IKT i helse- og sosialsektoren AS (www.KITH.no)

Cardiovascular disease_ICPC-2 Coding

ICPC-2 coding categories for different cardiovascular diseases.

K29	Cardiovascular Symptom/ Complaint other
K74	Ischaemic Heart Disease with Angina
K76	Atherosclerotic Heart Disease
K78	Atrial Fibrillation
K80	Cardiac Arrhythmia
K83	Heart Valve Disease
K84	Heart Disease/ Other
K89	Transient Cerebral Ischemia
K90	Stroke/ cerebral embolism/infarction/thrombosis/occlusion/ stenosis/hemorrhage
K92	Atherosclerosis/ Peripheral Vascular Disease
K93	Thromboembolism/Lung/ Pulmonary Embolism
K93	Portal Thrembosis/ superficial Deep Vein Thrombosis

Source: Kompetansesenter for IKT i helse- og sosialsektoren AS (www.KITH.no)

http://www.legemiddelsiden.no/default.aspx?PageID=706&ReportID=56&field=ICPC_Code&Value=F

Appendix 6. Calculations of Reductions in INR test GPs/ private specialist Visits per patient per year_Norway_2009-2011

Year	INR – Users Norway 2009-2013	INR-tests at GPs or private specialists	INR – tests Per warfarin-user	INR-tests with atrial fibrillation as main diagnosis	INR-tests with atrial fibrillation as main diagnosis-per user	INR –tests Per warfarin-user without atrial fibrillation	Visits with NOAC	Reduction in visits
2009	86319	929135	10,76	378109	4,38	6,38	(At least) 6,4	3,38
2010	88630	979100	11,04	399866	4,51	6,53	(At least) 6,5	3,51
2011	92131	1049014	11,38	444171	4,82	6,56	(At least) 6,6	3,82
2012	94709							
2013	87994							
2013 Kunnskaps-senteret-estimate,			13				5	8
At reimbursement application-Dabigatran,								16

Appendix 7. Visit reductions costs for 2009-2011, and Total NOACs costs for 2013 Norway

Costs associated with calculating number reduced INR-tests at GPs and private specialists' clinics in 2013 due to the introduction of NOACs for the treatment of atrial fibrillation, given the assumption that atrial fibrillation is the patients' main disease category, and that patients using NOACs need *only one control visit* to their doctor per year.

- Number of INR-measurements per warfarin- user =
  Number of INR measurements/ Number of users = (H11/G11) = 10.8
- Number of INR-measurements for patients with atrial fibrillation as main diagnosis per-user= INR-numbers for patients with atrial fibrillation as main diagnosis/ Number of users= (J11/G11)= 4.4
- INR-numbers per warfarin users at a GP without atrial fibrillation=
  (INR-numbers per warfarin-user)- (INR-numbers for patients with atrial fibrillation as main diagnosis per-user =(I 11-K11)
- Number of GPs visits with NOACs= (INR-numbers per warfarin users at a GP without atrial fibrillation)
- Reduction in GPs visits= (Number of INR-measurements for patients with atrial fibrillation as main diagnosis per-user) – (1)
- Cost per GPs visit (NOK)= 229 for 2009, 237 for 2010 and 244 for 2011
  Source: http://www.legemiddelsiden.no/default.aspx?PageID=139
- Reduced costs per patient= (Reduction)* (Cost per GPs visit) = (N11)*(O11)
- Total cost reductions= Reduced costs per patient (NOK) * number of users = (P11)*(G11)
- Estimated reduced total costs by the Kunnskapsseneret = (number of users)*(estimated numbers of GPs visits)*(costs per visit) = (G11)*(N$14)*(O11)

- **Total costs for Dabigatran in 2013 (NOK) = 9175*G20 = 9175*13 879 = 127 339 825**
- **Total costs for Rivaroxaban in 2013 (NOK) = 7966*G25 = 7966*13 423= 106 927 618**
- **Total costs for Apixaban in 2013 (NOK) = G30*9345 = 21 119 700**
- **Total costs NOACs in 2013 (NOK) = 255 387 143**
- **Total costs for warfarin in 2013 (NOK) = G15*901 = 87 994* 901= 79 282 594**
- **Total costs (NOACS and Warfarin) = 334 669 737**
- **Reimbursement costs for Dabigatran (NOK) =**
  G13*N$15*O13 = (94 709)*(16)*(244) = 359 679 424

Appendix 8. Number of Users_ Warfarin and NOACs_Total Costs_Norway 2009-2013

Number of users of all ages, both sexes in the entire country for Warfarin, Dabigatran, Rivaroxaban and Apixaban, in the period 2009-2013, and total costs of these drugs in 2013 (NOK).

Dabigatran, Rivaroxaban and Apixaban are referred to as new oral anticoagulants (NOACs)

Numbers of Users							
oral Anticoagulants	2009	2010	2011	2012	2013	Price per year (NOK)	Total Cost in 2013 (NOK)
Warfarin	86318	88630	92131	94709	87994	901	79 282 594
Dabigatran Etexilate	9	187	1168	4102	13879	9175	127 339 825
Rivaroxaban	45	191	898	1332	13423	7966	106 927 618
Apixaban	0	0	0	335	2260	9345	21 119 700
All 3 NOACs							255 387 143

Source: Norwegian Prescription Database

http://www.reseptregisteret.no

Report date: 29/05/2014 18:09

Total costs for Dabigatran in 2013 = =9175* 13 879 = 127 339 825
Total costs for Rivaroxaban in 2013= 7966* 13 423 = 106 927 618

Total costs for Apixaban in 2013= G30*9345 = 21 119 700

Reimbursement costs for Dabigatran= 94 709*16*244 = 359 679 424

Costs for Warfarin = 87 994* 901 = 79 282 594

Appendix 9. Reimbursement Costs Dabigatran_based on reduced visits-costs assumptions compared to HTA Kunnskapssenteret Report 5-2013

Year	Cost per visit	Reduced costs per patient	Reduced total costs based on calculated visits-reductions in this study	Reduced costs based on estimated visits-reductions given in the HTA Kunnskapssenteret Report 5-2013
2009	229	774,11	66 820 139	158 134 576
2010	237	832,27	73 762 932	168 042 480
2011	244	932,34	85 89 7760	179 839 712
At reimbursement application-Dabigatran				359 679 424

The formula used "in the Excel table" to calculate estimated reduced costs in the reimbursement application for Dabigatran:

G13*N$15*O13

Where,

a) G13: Number of users in 2013
b) N$15: Reduction in the number of patients' visits estimated by Boehringer-Ingelheim Pharma KG at their reimbursement application for Dabigatran
c) 244: cost of GPs, private specialists visit in 2013

= 92131*16*244

= 359 679 424 NOK

Appendix 10. Users of oral anticoagulants per 1000 (2004-2014)

Period	Users of oral anticoagulants/ total	Users/ total pr 1000
2004	43 596	19,1
2005	45 524	19,9
2006	47 168	20,4
2007	48 922	20,9
2008	50 322	21,2
2009	51 726	21,5
2010	53 315	21,8
2011	56 355	22,7
2012	59 809	23,8
2013	69 479	27,2
2014	72 165	27,9

Appendix 11. email survey

Kjære laboratorieleder/sjefsbioingeniør

Vi holder på med en studie der vi ønsker å beregne kostnadene ved INR-tester ved sykehus i Helse Sør-Øst. Disse data vil vi bruke i en helseøkonomisk analyse. Denne analysen er finansiert av legemiddelfirmaet Boehringer Ingelheim, Norge.

Vi tillater oss å spørre om du kunne gi oss tall for utførte antall INR-tester i 2009, gjerne fordelt etter poliklinikk, inneliggende, eller lignende. Vi regner med at det finnes rutinestatistikk for dette og håper at det ikke skal koste mye tid å svare på spørsmålet.

Dersom du ikke er rette person for å svare, ville vi være takknemlig for informasjon om hvem rette person er.

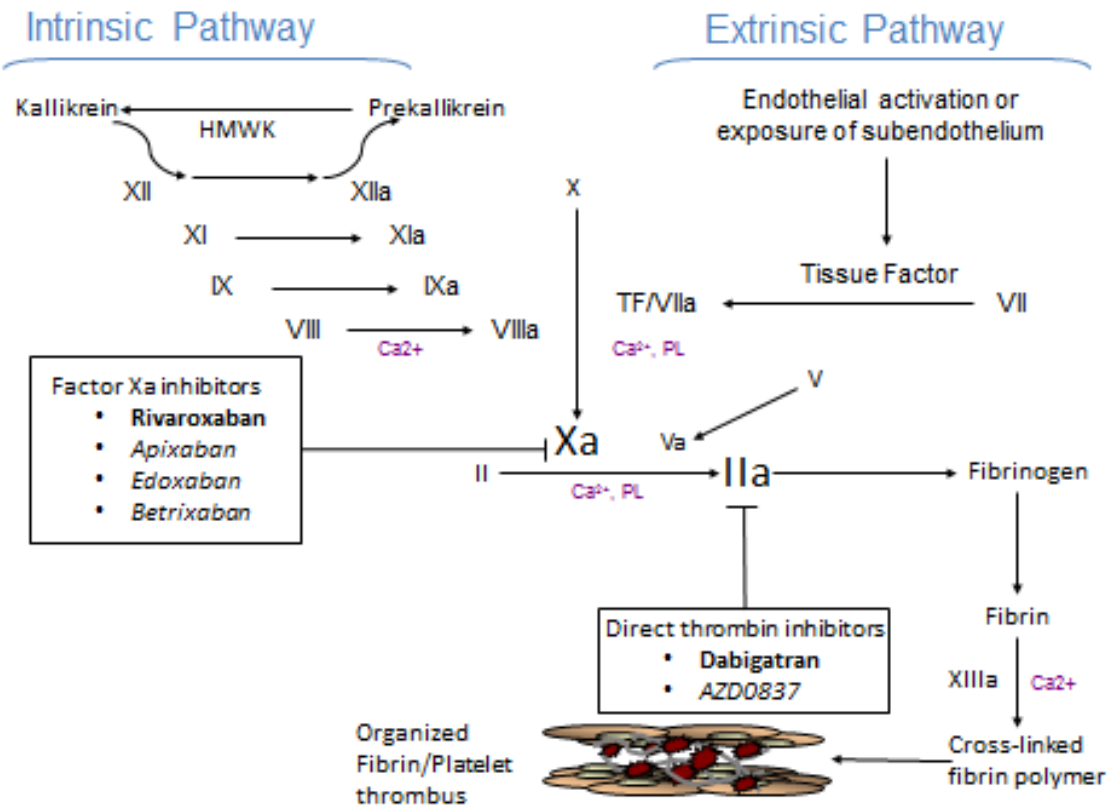
På forhånd takk for hjelpen.

Hani Murad
Masterstudent

Ivar Sønbø Kristiansen
professor

Avdeling for helseledelse og helseøkonomi, Universitetet i Oslo

Appendix 12. Coagulation cascades for different NOACs



Source:

http://www.mayoclinicproceedings.org/cms/attachment/2005915879/2026339620/mmc2.pdf

Appendix 13. Comparative Properties of Warfarin, Dabigatran, Rivaroxaban, and Apixaban

Characteristic	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Target	Vitamin K epoxide reductase	Factor IIa (free and clot-bound thrombin)	Factor Xa	Factor Xa
Prodrug	No	Yes	No	No
Bioavailability (%)	>95	6.5	>80	50
Metabolism	Hepatic, mainly via CYP2C9, CYP1A2, CYP3A4, CYP2C8, CYP2C18, and CYP2C19	Hepatic	Hepatic, mainly via CYP3A4, CYP3A5, and CYP2J2	Hepatic, mainly via CYP3A4 with minor contributions from CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2J2
Plasma protein binding (%)	97	34-35	~92-95 (primarily albumin)	87
Half-life (h)	40	14-17	5-9 9-13 (elderly)	10-14
Elimination	92% renal	80% renal 20% fecal	66% renal 33% fecal	27% renal 63% fecal
Monitoring	INR adjusted	Not needed	Not needed	Not needed
Peak effect (h)	72-96	2	2-4	3-4
Drug interactions	CYP2C9, CYP1A2, and CYP3A4	P-gp inducers/inhibitors	CYP3A4 and P-gp inducers/inhibitors	CYP3A4 and P-gp inducers/inhibitors
Antidote	Vitamin K	None	None	None
Reversal via hemodialysis	No	Yes	No	No

CYP = cytochrome; INR = international normalized ratio; P-gp = P-glycoprotein

Source: http://www.mayoclinicproceedings.org/article/S0025-6196(13)00222-X/fulltext#appsec1 (accessed 02.05.2015)

Appendix 14. Oral anticoagulant therapy: Recommended therapeutic Range

Indication	INR
Treatment of venous thrombosis	2.0–3.0
Treatment of pulmonary embolism	2.0–3.0
Prophylaxis of venous thrombosis (high-risk surgery)	2.0–3.0
Prevention of systemic embolism	2.0–3.0
Tissue heart valves	2.0–3.0
Acute myocardial infarction	2.0–3.0
Valvular heart disease	2.0–3.0
Atrial fibrillation	2.0–3.0
Bileaflet mechanical valve in aortic position	2.0–3.0
Mechanical prosthetic valves (high risk)	2.5–3.5
Systemic recurrent emboli	2.5–3.5

Source: Hirsh J, Dalen JE, Anderson DR, Poller L, Bussey H, Ansell J, Deykin D, Brandt JT. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 1998;114(5 Suppl):445S–469S.

Appendix 15. Number of users of Warfarin and NOACs per 1000 inhabitants between (2004- 2014). Rapport dato: 27.03.2015 11:50 http://www.reseptregisteret.no

		Number of users	Users pr 1000 inhabitants	Population baseline
B01AA03	2004	43 596	19,15	2 276 565
	2005	45 524	19,85	2 293 102
	2006	47 168	20,38	2 314 006
	2007	48 922	20,88	2 342 823
	2008	50 322	21,17	2 377 361
	2009	51 713	21,45	2 411 204
	2010	53 143	21,75	2 443 697
	2011	55 322	22,31	2 479 989
	2012	56 720	22,53	2 517 360
	2013	52 803	20,69	2 551 691
	2014	46 709	18,08	2 583 218
B01AE07	2004	0	0,00	0
	2005	0	0,00	0
	2006	0	0,00	0
	2007	0	0,00	0
	2008	0	0,00	0
	2009	7	0,00	2 411 204
	2010	106	0,04	2 443 697
	2011	669	0,27	2 479 989
	2012	2 349	0,93	2 517 360
	2013	8 288	3,25	2 551 691
	2014	9 329	3,61	2 583 218
B01AF01	2004	0	0,00	0
	2005	0	0,00	0
	2006	0	0,00	0
	2007	0	0,00	0
	2008	0	0,00	0
	2009	6	0,00	2 411 204
	2010	66	0,03	2 443 697
	2011	364	0,15	2 479 989
	2012	609	0,24	2 517 360
	2013	7 350	2,88	2 551 691
	2014	11 584	4,48	2 583 218
B01AF02	2004	0	0,00	0
	2005	0	0,00	0
	2006	0	0,00	0
	2007	0	0,00	0
	2008	0	0,00	0
	2009	0	0,00	0
	2010	0	0,00	0
	2011	0	0,00	0
	2012	131	0,05	2 517 360
	2013	1 038	0,41	2 551 691
	2014	4 543	1,76	2 583 218

Valgte søkekriterier:
Legemiddel:
- B01AA03 -warfarin
- B01AE07 -dabigatran eteksilat
- B01AF01 -rivaroksaban
- B01AF02 -apixaban

Periode: 2014, 2013, 2012, 2011, 2010, 2009, 2008, 2007, 2006, 2005, 2004
Kjønn: Mann
Ikke valgte søkekriterier:

Alder: tallene i rapporten er for alle aldre
Bosted: tallene i rapporten er for hele landet

Appendix 16. Total umber of ususersof Oral anti coagulants per 1000 inhabitants between (2004- 2014). SUMMARY OUTPUT

Regression Statistics	
Multiple R	0,98456
R Square	0,969358
Adjusted R Square	0,961697
Standard Error	0,169515
Observations	6

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	3,636121	3,636121	126,538	0,000356
Residual	4	0,114942	0,028735		
Total	5	3,751063			

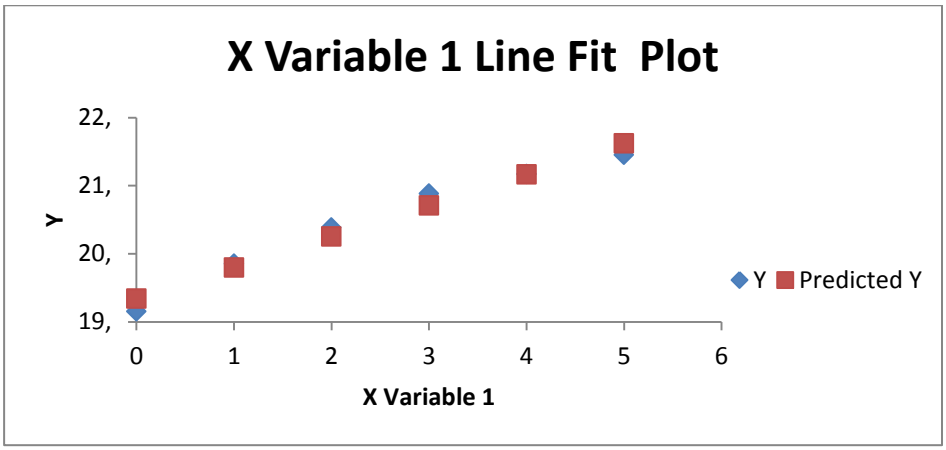
	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	19,34166	0,122686	157,6516	9,71E-09	19,00103	19,68229	19,00103	19,68229
X Variable 1	0,455827	0,040522	11,24891	0,000356	0,34332	0,568334	0,34332	0,568334

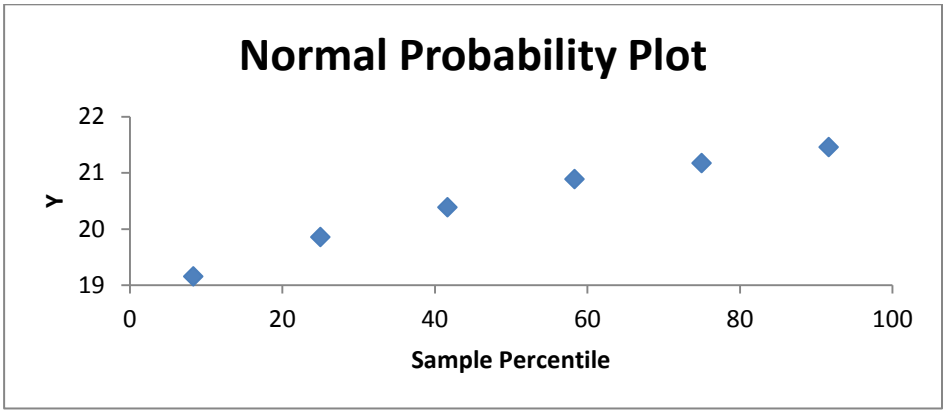
RESIDUAL OUTPUT

Observation	*Predicted Y*	*Residuals*
1	19,34166	-0,19175
2	19,79748	0,055099
3	20,25331	0,130386
4	20,70914	0,172507
5	21,16497	0,002202

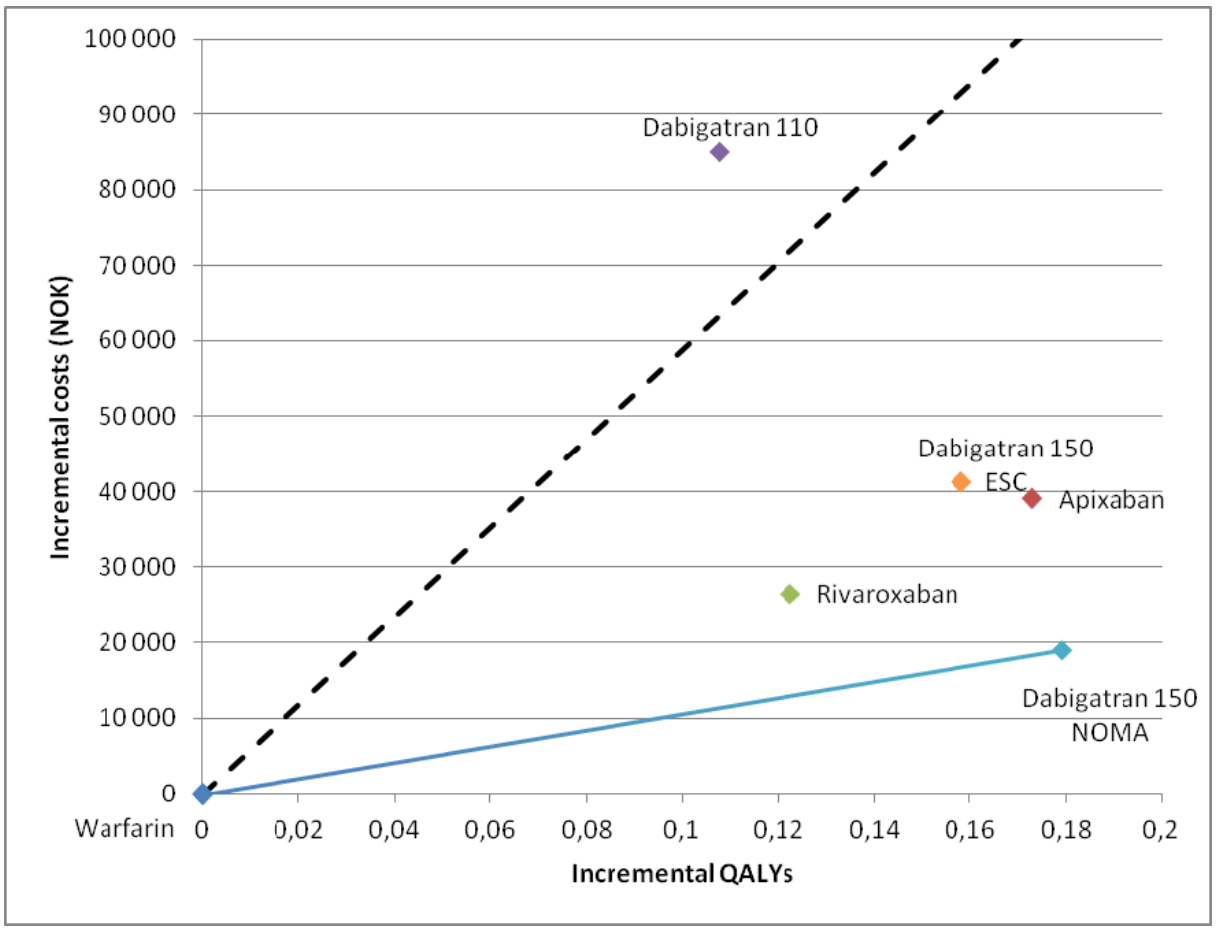
PROBABILITY OUTPUT

Percentile	*Y*
8,333333	19,1499
25	19,85258
41,66667	20,3837
58,33333	20,88165
75	21,16717


X Variable 1 Line Fit Plot
22,
21,
20,
19,
Y
0
1
2
3
4
5
6
X Variable 1
Y
Predicted Y


Normal Probability Plot
22
21
20
19
Y
0
20
40
60
80
100
Sample Percentile

Appendix 17. Mean incremental costs and effects for new oral anticoagulants compared to warfarin, (dotted line represents WTP)



Source: HTA-13 Report, page 48